

FORM PTO-1390 (Modified)
(REV 11-98)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES

205559US0PCT

DESIGNATED/ELECTED OFFICE (DO/EO/US)

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

CONCERNING A FILING UNDER 35 U.S.C. 371

09/830668

INTERNATIONAL APPLICATION NO.

PCT/EP99/08307

INTERNATIONAL FILING DATE

27 OCTOBER 1999

PRIORITY DATE CLAIMED

30 OCTOBER 1998

TITLE OF INVENTION

2-UREIDO-THIAZOLE DERIVATIVES, PROCESS FOR THEIR PREPARATION, AND THEIR USE AS ANTITUMOR AGENTS

APPLICANT(S) FOR DO/EO/US

Paolo PEVARELLO, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

Request for Consideration of Documents Cited in International Search Report

Notice of Priority

PCT/IB/304

PCT/IB/308

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205559US0 PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :
PAOLO PEVARELLO ET AL : ATTN: APPLICATION DIVISION
SERIAL NO: NEW US PCT APPLN. :
(Based on PCT/EP99/08307)
FILED: HERewith :
FOR: 2-UREIDO-THIAZOLE :
DERIVATIVES, PROCESS FOR :
THEIR PREPARATION, AND :
THEIR USE AS ANTITUMOR :
AGENTS :

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Prior to examination on the merits, please amend the above-identified application as follows.

IN THE CLAIMS

Please cancel Claims 5 and 13.

Please add the following claims:

17. (New) Use according to claim 1 wherein the medicament enables tumor angiogenesis and metastasis inhibition.

18. (New) A compound of formula (I) according to claim 6, whenever appropriate in the form of pharmaceutically acceptable salts, selected from the group consisting of:

- 1) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-phenyl-urea;
- 2) N-(5-bromo-1,3-thiazol-2-yl)-N'-phenyl-urea;
- 3) N-(5-phenyl-1,3-thiazol-2-yl)-N'-phenyl-urea;
- 4) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-phenyl-urea;
- 5) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)urea;
- 6) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)urea;
- 7) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)urea;
- 8) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-sulfamoylphenyl)-urea;
- 9) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)urea;
- 10) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)urea;
- 11) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)urea;
- 12) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-methoxyphenyl)-urea;
- 13) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)urea;
- 14) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-urea;
- 15) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)urea;
- 16) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-chlorophenyl)-urea;
- 17) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)urea;
- 18) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;
- 19) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;
- 20) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-chlorophenyl)-urea;
- 21) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-urea;
- 22) N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-urea;
- 23) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-urea;
- 24) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-chlorophenyl)-urea;

- 25) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)urea;
- 26) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)urea;
- 27) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)urea;
- 28) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-methoxyphenyl)-urea;
- 29) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)urea;
- 30) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)urea;
- 31) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)urea;
- 32) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-hydroxyphenyl)-urea;
- 33) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)urea;
- 34) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)urea;
- 35) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)urea;
- 36) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-hydroxyphenyl)-urea;
- 37) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)urea;
- 38) N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)urea;
- 39) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)urea;
- 40) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-urea;
- 41) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-urea;
- 42) N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)urea;
- 43) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)urea;
- 44) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-hydroxyphenyl)-urea;
- 45) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)urea;
- 46) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-urea;
- 47) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-urea;
- 48) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)urea;

- 49) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)urea;
- 50) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-urea;
- 51) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-urea;
- 52) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-urea;
- 53) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)urea;
- 54) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-urea;
- 55) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-urea;
- 56) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)urea;
- 57) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-urea;
- 58) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-urea;
- 59) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-urea;
- 60) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)urea;
- 61) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
- 62) N-(5-bromo-1,3-thiazol-2-yl)-N'-benzyl-urea;
- 63) N-(5-phenyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
- 64) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
- 65) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
- 66) N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
- 67) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
- 68) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
- 69) N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
- 70) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
- 71) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
- 72) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)urea;

73) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;

74) N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;

75) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;

76) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)urea;

77) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(benzothiophen-2yl)-urea;

78) N-(5--bromo-1,3-thiazol-2-yl)-N'-(benzothiophen-2-yl)-urea;

79) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(benzothiophen-2-yl)-urea;

N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(benzothiophen-2-yl)-urea;

80) N-(5-isopropyl-1,3-thiazol-2-yl)-4-morpholine carboxamide;

81) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methylphenyl)urea;

82) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-fluorophenyl)urea;

83) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-cyanophenyl)urea;

84) N-(5-isopropyl-2,3-thiazol-2-yl)-N'-(3-cyanophenyl)urea;

85) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,6-dimethylphenyl)urea;

86) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-fluorobenzyl)urea;

87) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-acetylphenyl)urea;

88) N-(5-isopropyl-2,3-thiazol-2-yl)-N'-(4-acetylphenyl)urea;

89) 3-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)benzoic acid;

90) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-isopropylphenyl)urea;

91) 3-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)benzamide;

92) N-(5-isopropyl-1,3-thiazol-2-yl)-N'(4-methoxybenzyl)urea;

93) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-butylphenyl)urea;

94) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-trifluoromethylphenyl)urea;

95) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-3-bromophenyl)urea;

- 96) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-cyclohexylphenyl)urea;
- 97) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-phenoxyphenyl)urea;
- 98). N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-benzyloxyphenyl)urea;
- 99) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-dimethylphenyl)urea;
- 100) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,3-dimethylphenyl)urea;
- 101) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-methoxy[1,1'-biphenyl]-4-yl)urea;
- 102) N-(5-isopropyl-1,3-thiazol-2-yl)-3,4-dihydro-2(1H)-isoquinoline carboxamide;
- 103) N-benzyl-N-(5-isopropyl-1,3-thiazol-2-yl)-N'-methylurea;
- 104) N-(5-isopropyl-1,3-thiazol-2-yl)-6,7-dimethoxy-3,4-dihydro-2(1H)-isoquinoline carboxamide;
- 105) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(3-chloro-4-methyl)-phenyl]urea;
- 106) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(3-chloro-6-methyl)phenyl]urea;
- 107) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-dimethoxyphenyl)urea;
- 108) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-dimethoxyphenyl)urea;
- 109) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(2-methoxy-5-chloro)phenyl]urea;
- 110) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-((2-chloro-4-methoxyphenyl)urea;
- 111) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-dichlorophenyl)urea;
- 112) N-[(1,1-biphenyl)-2-yl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 113) N-ethyl-N-(5-isopropyl-1,3-thiazol-2-yl)-N'-phenylurea;
- 114) N-[4-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)-2-methoxyphenyl]acetamide;
- 115) 2-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)-N-phenylbenzamide;
- 116) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-morpholinophenyl)urea;

117) N-[4-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)phenyl]-N'-methyl

acetamide;

118) N-(2-{[cyclohexyl(methyl)amino]methyl}phenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;

119) N-[3-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)-4-

methoxyphenyl]acetamide;

120) N-(5-isopropyl-1,3-thiazol-2-yl)-4-(4-methoxyphenyl)-1-piperazine carboxamide;

121) N-(2-furylmethyl)-N'-(5-isopropyl-1,3-thiazol-2-yl) urea ;

122) N-(4-fluorophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;

123) N-(2-methoxybenzyl)-N'-(5-isopropyl-1,3-thiazol-2-yl) urea;

124) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[2-(1-methyl-1H-pyrrol-2-yl)ethyl]urea;

125) N-(3,4-dimethoxybenzyl)-N'-(5-isopropyl-1,3-thiazol-2-yl) urea ;

126) N-(5-isopropyl-1,3-thiazol-2-yl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane-8-carboxamide;

127) n-(5-isopropyl-1,3-thiazol-2-yl)-1,4-dioxo-8-azaspiro[4.5]decane-8-carboxamide;

128) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[2-(1-piperidiny)ethyl]urea;

129) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[2-(1-morpholiny)ethyl]urea;

130) 4-(4-fluorophenyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperazine carboxamide;

131) N-[4-(4-chlorophenyl)-3-ethyl-5-isoxazolyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;

132) 4-[(4-fluorophenyl)(hydroxy)methyl]-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperidine carboxamide;

133) N-(3-ethynylphenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;

134) N-(2-methoxy-3-fluorophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;

135) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-oxo-1-piperidiny)urea;

136) N-(3-acetylamino)phenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;

- 137) N-[3-(2-furyl)-1H-pyrazol-5-yl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 138) N-{4-[ethyl(isopropyl)amino] phenyl}-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 139) N-(1,3-benzodioxol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 140) 5-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl} amino)-1-phenyl-1H-pyrazole-4-carboxamide;
- 141) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-pyridinylmethyl)urea;
- 142) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-pyrazinyl)urea;
- 143) n-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-phenyl-1,3,4-oxadiazol-2-yl)urea;
- 144) N-(5-isopropyl-1,3-thiazol-2-yl)-4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-piperidine carboxamide;
- 145) N-(1,3-benzothiazol-6-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 146) N-(1,3-dimethyl-1H-pyrazol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 147) N-(3-phenyl-1-methyl-1H-pyrazol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 148) N-(5-isopropyl-1,3-thiazol-2-yl)-3-hydroxy-1-piperidine carboxamide;
- 149) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)urea;
- 150) N-(5-isopropyl-1,3-thiazol-2-yl)-4-benzyl-1-piperazine carboxamide;
- 152) N-(5-isopropyl-1,3-thiazol-2-yl)-4-methyl-1-piperazine carboxamide;
- 152) 4-hydroxy-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperidine carboxamide;
- 153) N-(5-isopropyl-1,3-thiazol-2-yl)-3-azabicyclo[3.2.2]nonane-3-carboxamide;
- 154) N-(5-isopropyl-1,3-thiazol-2-yl)-4-(4-acetylphenyl)-1-piperazine carboxamide;
- 155) 4-[bis(4-fluorophenyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperazine carboxamide;
- 156) N-(5-isopropyl-1,3-thiazol-2-yl)-4-oxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide;

- 157) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5,6,7,8-tetrahydro-1-naphtalenyl)urea;
- 158) N-(4-phenyl-2-thiazolyl)-N'-(5-isopropyl-1,3-thiazol-2-yl) urea;
- 159) 4-(4-fluorobenzoyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperidine carboxamide;
- 160) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-1,3-dihydro-2-benzofuran-5-yl)urea;
- 161) N-(5-isopropyl-1,3-thiazol-2-yl)-4'-(2-pyrimidinyl)-1-piperazine carboxamide;
- 162) N-(5-isopropyl-1,3-thiazol-2-yl)-3-oxo-3,4-dihydro-1(2H)-quinoxaline;
- 163) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1H-indazol-6-yl)urea;
- 164) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-chlorobenzyl)urea;
- 165) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dichlorobenzyl)urea;
- 166) N-(5 isopropyl-1,3-thiazol-2 yl)-N'-(3-fluorobenzyl)urea;
- 167) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-dichlorobenzyl)urea;
- 168) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-difluorobenzyl)urea;
- 169) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-difluorobenzyl)urea;
- 170) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-2,6-difluorobenzyl)urea;
- 171) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(4-hydroxy-3-methoxy)benzyl]urea;
- 172) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-methyl-2-furyl)urea;
- 173) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methylsulfonylbenzyl)urea;
- 174) N-[(1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 175) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-chlorobenzyl)urea;
- 176) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-pyridinylmethyl)urea;
- 177) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-dimethoxybenzyl)urea;
- 178) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-pyridinylmethyl)urea;
- 179) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-trifluorobenzyl)urea;
- 180) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4,5-trimethoxybenzyl)urea;

- 181) N-(5-isopropyl-1,3-thiazol-2-yl)-N-(2,4-dimethoxybenzyl)urea;
- 182) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-dimethylaminobenzyl)urea;
- 183) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-dimethoxybenzyl)urea;
- 184) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(2-chloro-6-phenoxy)benzyl]urea;
- 185) N-(5-isopropyl-2,3-thiazol-2-yl)-N'-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]urea;
- 186) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(3-hydroxy-4-methyl)phenyl]urea;
- 187) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[4-(1H-benzimidazol-2-yl)phenyl]urea;
- 188) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-phenyl-1H-pyrazol-5-yl)urea;
- 189) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methyl-6-guinoliny)urea;
- 190) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[4-(cyanomethyl)phenyl]urea;
- 191) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-quinoliny)urea;
- 192) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1-oxo-2,3-dihydro-1H-inden-5-yl)urea;
- 193) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-oxo-1,3-dihydro-2-benzofuran-5-yl)urea;
- 194) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-oxo-5,6,7,8-tetrahydro-2-naphtalenyl)urea;
- 195) methyl-3-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)-4-methylbenzoate;
- 196) methyl-4-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)-3-methylbenzoate;
- 197) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-imidazo[1,2-a]pyridin-2-yl-phenyl)urea;
- 198) ethyl-4-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)benzoate;
- 199) (2R)-1-benzyl-2-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)propanamide;
- 200) 2-hydroxy-5-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}benzoic acid;
- 201) 2-chloro-5-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)benzoic acid;
- 202) 3-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)benzoic acid;
- 203) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-methyl-3-isoxazolyl)urea;
- 204) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,6-dimethoxyphenyl)urea;

- 205) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,3-dimethoxybenzyl)urea;
- 206) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-difluorobenzyl)urea;
- 207) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dimethylphenyl)urea;
- 208) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1H-benzimidazol-5-yl)urea;
- 209) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(R)-phenylglycinamido]urea;
- 210) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-phenoxyacetamido)urea;
- 211) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(S)-phenylglycinamido]urea;
- 212) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-{2-[(1-methyl-1H-imidazol-2-yl)methoxy]phenyl}urea;
- 213) N-(3-iodophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 214) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-j3-(3-methoxy-1-propynyl)phenyl]urea;
- 215) N-{3-[3-(dimethylamino)-1-propynyl]phenyl}-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 216) N-[4-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)phenyl]methanesulfonamide;
- 217) 2-[3-({[(5-isopropyl-1,3-thiazol-2-ylamino)carbonyl]amino)anilino]acetamide;
- 218) N-[3-(3-hydroxy-1-butynyl)phenyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 219) N-(imidazol-2-yl)pyridin-2-yl-methyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 220) 2-{[[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}(2-propynyl)amino]methyl}benzenesulfonamide;
- 221) N-(1H-indol-6-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 222) N-j(1S)-2-hydroxy-1-phenylethyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 223) N-(1H-indol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 224) N-[(1R-2-hydroxy-1-phenylethyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 225) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-butylurea;


- 226) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-benzoylurea;
- 227) N-(5-methyl-1,3-thiazol-2-yl)-N'-(2,6-dimethylphenyl)urea;
- 228) N-(5-methyl-1,3-thiazol-2-yl)-N'-benzylurea;
- 229) N-(5-methyl-1,3-thiazol-2-yl)-N'-butylurea;
- 230) N-(5-methyl-1,3-thiazol-2-yl)-4-morpholinecarboxamide;
- 231) N-(5-methyl-1,3-thiazol-2-yl)-N'-phenylurea;
- 232) N-(5-methyl-1,3-thiazol-2-yl)-N'-(4-methoxybenzylurea);
- 233) N-(5-methyl-1,3-thiazol-2-yl)-N'-(4-fluorophenyl)urea;
- 234) N-[(1-ethyl-2-pyrrolidinyl)methyl]-N'-(5-methyl-1,3-thiazol-2-yl)urea;
- 235) N-(5-methyl-1,3-thiazol-2-yl)-N'-(5-hydroxy-1H-pyrazol-3-yl)urea;
- 236) N-(5-methyl-1,3-thiazol-2-yl)-N'-(3-pyridinyl)urea;
- 237) N-(4-fluorophenyl)-N'-(5-methyl-1,3-thiazol-2-yl)urea.--

REMARKS

Claims 1-4, 6-12 and 14-18 are active in the application. The claims are amended to remove multiple dependencies. Claim 17 finds support in Claim 5 and Claim 18 finds support in Claim 13. No new matter is added. An action on the merits and allowance of the claims is solicited.

Respectfully submitted,

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-1-

2-UREIDO-THIAZOLE DERIVATIVES, PROCESS FOR THEIR
PREPARATION, AND THEIR USE AS ANTITUMOR AGENTS

5

The present invention relates to 2-ureido-thiazole derivatives and, more in particular, it relates to 2-ureido-1,3-thiazoles, to a process for their preparation, to pharmaceutical compositions containing them and to their
10 use as therapeutic agents, particularly in the treatment of cancer and cell proliferative disorders.

Several cytotoxic drugs such as, e.g. fluorouracil (5-FU), doxorubicin and camptothecins result to damage DNA or to
15 affect cellular metabolic pathways and thus cause, in many cases, an indirect block of the cell cycle.

Therefore, by producing an irreversible damage to both normal and tumor cells, these agents result in a significant toxicity and side-effects.

20 In this respect, compounds capable of being highly specific antitumor agents by selectively leading to tumor cell arrest and apoptosis, with comparable efficacy but reduced toxicity than the currently available drugs, are desirable.

25 It is well known in the art that progression through the cell cycle is governed by a series of checkpoint controls, otherwise referred to as restriction points, which are regulated by a family of enzymes known as the cyclin-dependent kinases (cdk).

30 In their turn, the cdks themselves are regulated at many levels such as, for instance, binding to cyclins.

A normal progression through the cell cycle is controlled by the coordinated activation and inactivation of different cyclin/cdk complexes. In G1, both cyclin D/cdk4 and cyclin
35 E/cdk2 are thought to mediate the onset of S-phase. Progression through S-phase requires the activity of cyclin A/cdk2 whereas the activation of cyclin A/cdc2 (cdk1) and cyclin B/cdc2 are required for the onset of metaphases.

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For a general reference to cyclins and cyclin-dependent kinases see, for instance, Kevin R. Webster et al. in Exp. Opin. Invest. Drugs, 1998, Vol. 7(6), 865-887.

- 5 Checkpoint controls are defective in tumor cells due, in part, to dysregulation of cdk activity. For example, altered expression of cyclin E and cdk's has been observed in tumor cells, and deletion of the cdk inhibitor p27 KIP gene in mice has been shown to result in a higher incidence
10 of cancer.

Increasing evidence supports the idea that the cdks are rate-limiting enzymes in cell cycle progression and, as such, represent molecular targets for therapeutic intervention. In particular, the direct inhibition of
15 cdk/cyclin kinase activity should be helpful in restricting the unregulated proliferation of a tumor cell.

It has now been found that the 2-ureido-1,3-thiazoles of the invention are endowed with cdk/cyclin kinase inhibitory
20 activity and are thus useful in therapy as antitumor agents whilst lacking, in terms of both toxicity and side effects, the aforementioned drawbacks known for currently available antitumor drugs.

More specifically, the compounds of this invention are
25 useful in the treatment of a variety of cancers including, but not limited to: carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous
30 cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of
35 myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central

and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, 5 thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of cdks in the regulation of cellular proliferation, these 2-ureido-1,3-thiazole derivatives are also useful in the treatment of a variety of cell 10 proliferative disorders such as, for instance, benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis, glomerulonephritis and post-surgical 15 stenosis and restenosis.

The compounds of the invention can be useful in the treatment of Alzheimer's disease, as suggested by the fact that cdk5 is involved in the phosphorylation of tau protein (*J.Biochem.*, 117, 741-749, 1995).

20 The compounds of this invention, as modulators of apoptosis, could be useful in the treatment of cancer, viral infections, prevention of AIDS development in HIV-infected individuals, autoimmune diseases and neurodegenerative disorder.

25 The compounds of this invention could be useful in inhibiting tumor angiogenesis and metastasis.

The compounds of this invention may also act as inhibitors of other protein kinases, e.g. protein kinase C, her2, 30 raf1, MEK1, MAP kinase, EGF receptor, PDGF receptor, IGF receptor, PI3 kinase, weel kinase, Src, Abl and thus be effective in the treatment of diseases associated with other protein kinases.

35 Several 2-ureido-1,3-thiazole derivatives are known in the art, particularly as herbicides or as synthetic intermediates for preparing herbicides [see, for a general

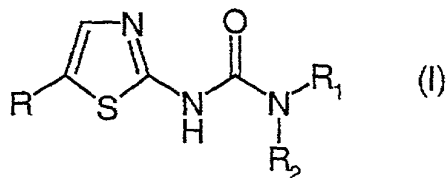
reference, US 3,726,891 in the name of Shell Co., and C.A. 83(1975):114381].

Just few examples among them are N'-methyl- and N'-ethyl-N-(5-bromo-2-thiazolyl)-urea; N'-methyl-, N'-ethyl- or N'-phenyl-N-(5-chloro-2-thiazolyl)-urea; N-(5-chloro-2-thiazolyl)-N',N'-dimethyl-urea; N-(5-bromo-2-thiazolyl)-N',N'-dimethyl-urea; N'-methyl- and N'-phenyl-N-(5-methyl-2-thiazolyl)-urea.

Other 2-ureido-1,3-thiazole derivatives have been described in the art as therapeutic agents.

Among them are N-methyl- and N-phenyl-N'-(5-chloro-2-thiazolyl)-urea which have been described as sedative and antiinflammatory agents in FR M. 7428 (Melle-bezons) or N-[4-(5-oxazolyl)phenyl]-N'-(5-methyl-2-thiazolyl)-urea, described as inosine 5'-monophosphate dehydrogenase inhibitor (IMPDH) in WO 97/40028 (Vertex Pharmaceuticals Inc.).

Accordingly, the present invention provides the use of a compound which is a 2-ureido-1,3-thiazole derivatives of formula (I)



wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

- i) straight or branched C₁-C₆ alkyl;
- ii) C₃-C₆ cycloalkyl;
- iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R₁ is an optionally further substituted group selected from:

- i), straight or branched C₁-C₆ alkyl;

ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;

iii) aryl or arylcarbonyl;

iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R_2 is hydrogen, a straight or branched C_1-C_4 alkyl or C_2-C_4 alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

R_1 and R_2 form a substituted or unsubstituted group selected from:

i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or

ii) a 9 to 11 membered spiro-heterocyclic compound;

or a pharmaceutically acceptable salt thereof; in the manufacture of a medicament for treating cell proliferative disorders associated with an altered cell dependent kinase activity.

According to a preferred embodiment of the invention, the said cell proliferative disorder is selected from the group consisting of cancer, Alzheimer's disease, viral infections, auto-immune diseases or neurodegenerative disorders.

Preferably, the cancer is selected from the group consisting of carcinoma, squamous cell carcinoma, hematopoietic tumors of myeloid or lymphoid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratocanthoma, thyroid follicular cancer and Kaposi's sarcoma.

According to another preferred embodiment of the invention, the cell proliferative disorder is selected from the group consisting of benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis

glomerulonephritis and post-surgical stenosis and restenosis.

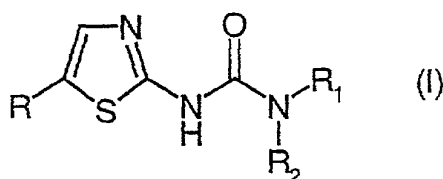
In addition, being useful in the treatment of cell proliferative disorders associated with an altered cell dependent kinase activity, hence cell cycle inhibition or cdk/cyclin dependent inhibition, the compounds of formula (I) of the invention also enable tumor angiogenesis and metastasis inhibition.

10

As above reported, some of the compounds of formula (I) of the invention have been reported in the art as useful therapeutic agents, for instance as antiinflammatory, sedative and analgesic agents.

15

Therefore, it is a further object of the present invention a compound which is a 2-ureido-1,3-thiazole derivative of formula (I)



20 wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

- i) straight or branched C₁-C₆ alkyl;
25 ii) C₃-C₆ cycloalkyl;
iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R₁ is an optionally further substituted group selected from:

- 30 i) straight or branched C₁-C₆ alkyl;
ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;
iii) aryl or arylcarbonyl;

iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R_2 is hydrogen, a straight or branched C_1 - C_6 alkyl or C_2 - C_6 alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

R_1 and R_2 form a substituted or unsubstituted group selected from:

i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or

ii) a 9 to 11 membered spiro-heterocyclic compound; or a pharmaceutically acceptable salt thereof;

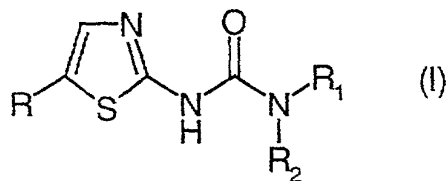
for use as a medicament; provided that:

a) when R is a chlorine atom and R_2 is hydrogen, then R_1 is not methyl, phenyl or trifluoromethylphenyl; and

b) when R is methyl and R_2 is hydrogen, then R_1 is not 4-(5-oxazolyl)phenyl.

Among the compounds of formula (I) above reported, several derivatives result to be novel.

Therefore, the present invention further provides a compound which is a 2-amino-1,3-thiazole derivative of formula (I)



wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

i) straight or branched C_1 - C_6 alkyl;

iii) C_3 - C_6 cycloalkyl;

iv) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R_1 is an optionally further substituted group selected from:

- i) straight or branched C_1-C_6 alkyl;
ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;
iii) aryl or arylcarbonyl;
5 iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;
 R_2 is hydrogen, a straight or branched C_1-C_4 alkyl or C_2-C_4 alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,
10 R_1 and R_2 form a substituted or unsubstituted group selected from:
i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or
ii) a 9 to 11 membered spiro-heterocyclic compound; or a
15 pharmaceutically acceptable salt thereof; provided that:
a) when R is chlorine or bromine and R_2 is hydrogen, then R_1 is not unsubstituted C_1-C_3 alkyl, phenyl, trifluoromethylphenyl or an optionally substituted phenylcarbonyl;
20 b) when R is methyl and R_2 is hydrogen, then R_1 is not methyl, phenyl or 4-(5-oxazolyl)phenyl;
c) when R is nitrophenyl and R_2 is hydrogen, then R_1 is not haloalkyl;
d) when R is bromine or chlorine, then R_1 and R_2 are not
25 both methyl groups.

The compounds of formula (I) may have asymmetric carbon atoms and may therefore exist either as racemic admixtures or as individual optical isomers.

- 30 Accordingly, all the possible isomers and their admixtures and of both the metabolites and the pharmaceutically acceptable bio-precursors (otherwise referred to as pro-drugs) of the compounds of formula (I), as well as the uses thereof, are also within the scope of the present
35 invention.

In the present description, unless otherwise specified, with the term halogen atom we intend a chlorine, bromine, fluorine or iodine atom.

- 5 With the term optionally substituted amino group we intend an amino group wherein one or both hydrogen atoms are optionally replaced by other substituents which are the same or different, as set forth below.
- 10 With the term straight or branched C_1 - C_6 alkyl we intend a group such as, for instance, methyl, ethyl, n.propyl, isopropyl, n.butyl, isobutyl, sec-butyl, tert-butyl, n.pentyl, n.hexyl and the like.
- 15 With the term straight or branched C_2 - C_4 alkenyl or alkynyl group we intend a group such as, for instance, vinyl, allyl, isopropenyl, 1-, 2- or 3-butenyl, isobutylene, ethynyl, 1- or 2-propynyl, butynyl and the like.
- 20 With the term C_3 - C_6 cycloalkyl we intend a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

- With the term aryl, either as such or as arylalkyl, arylcarbonyl and the like, we intend a mono-, bi- or poly-
- 25 either carbocyclic as well as heterocyclic hydrocarbon with from 1 to 4 ring moieties, either fused or linked to each other by single bonds, wherein at least one of the carbocyclic or heterocyclic rings is aromatic.

- Examples of aryl groups are phenyl, biphenyl, α - or β -
- 30 naphthyl, tetrahydronaphthyl, indenyl, dihydroindenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, dihydroisoindolyl, imidazolyl, imidazopyridyl, benzimidazolyl, dihydrobenzimidazolyl, 1,2-methylenedioxyphenyl, thiazolyl, isothiazolyl,
- 35 benzothiazolyl, pyrrolyl, pyrazolyl, furyl, benzotetrahydrofuran, benzofuran, dihydrobenzofuran, oxazolyl, isoxazolyl, thienyl, benzothienyl, tetrazolyl,

quinolinyl, isoquinolinyl, dihydroisoquinolinyl,
quinoxalinyl, dihydroquinoxalinyl, oxadiazolyl,
tetrahydrobenzodiazepin-yl and the like.

5 With the term 3 to 6 membered carbocycle, hence encompassing but not limited to C₃-C₆ cycloalkyl groups, we also intend an unsaturated carbocyclic hydrocarbon such as, for instance, cyclopentylene or cyclohexylene.

10 With the term 5 to 7 membered heterocycle, hence encompassing aromatic heterocycles also referred to as aryl groups, we further intend a saturated or partially unsaturated 5 to 7 membered carbocycle wherein one or more carbon atoms are replaced by heteroatoms such as nitrogen,
15 oxygen and sulphur.

Examples of 5 to 7 membered heterocycles, optionally benzocondensed or further substituted, are 1,3-dioxolane, pyran, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, piperidine, piperazine, N-alkyl-piperazine,
20 morpholine, tetrahydrofuran, and the like.

With the term bridged heterocycles we intend a system at least comprising two rings, one of which being a nitrogen containing heterocycle, having two or more atoms in common
25 such as, for instance, azabicyclo[3.2.2]nonane.

With the term 9 to 11 membered spiro heterocycle we intend a system at least comprising two rings, one of which being a nitrogen containing heterocycle, having one carbon atom
30 in common such as, for instance, 1,4-dioxa-8-azaspiro[4.5]decane and 1,3,8-triazaspiro[4.5]decane.

According to the above indicated substituent meanings, any of the above R, R₁ and R₂ groups may be optionally
35 substituted in any of the free positions by one or more groups, for instance 1 to 6 groups, selected from: halogen, nitro, oxo groups (=O), carboxy, cyano, alkyl, perfluorinated alkyl, alkenyl, alkynyl, cycloalkyl, aryl,

heterocyclyl, amino groups and derivatives thereof such as, for instance, alkylamino, alkoxy carbonyl alkylamino, dialkylamino, arylamino, diarylamino, alkylsulfonylamino or arylureido; carbonylamino groups and derivatives thereof
5 such as, for instance, formylamino, alkylcarbonylamino, alkenylcarbonylamino, arylcarbonylamino, alkoxy carbonylamino; oxygen-substituted oximes such as, for instance, alkoxy carbonyl alkoxyimino or alkoxyimino; hydroxy groups and derivatives thereof such as, for instance,
10 alkoxy, aryloxy, alkylcarbonyloxy, arylcarbonyloxy, cycloalkenyloxy; carbonyl groups and derivatives thereof such as, for instance, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aryloxy carbonyl, cycloalkyloxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl;
15 sulfurated derivatives such as, for instance, alkylthio, arylthio, alkylsulphonyl, arylsulphonyl, alkylsulphinyl, arylsulphinyl, arylsulphonyloxy, aminosulfonyl, alkylaminosulphonyl or dialkylaminosulphonyl. In their turn, whenever appropriate, each of the above possible
20 substituents on R, R₁ and R₂ may be further substituted by one or more of the aforementioned groups.

Examples of compounds of formula (I) wherein R, R₁ and R₂ groups are substituted by one or more of the aforementioned substituents which, in their turn, are optionally further
25 substituted as set forth above, are given below.

Pharmaceutically acceptable salts of the compounds of formula (I) are the acid addition salts with inorganic or organic, e.g. nitric, hydrochloric, hydrobromic, sulphuric,
30 perchloric, phosphoric, acetic, trifluoroacetic, propionic, glycolic, lactic, oxalic, malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic, methanesulphonic, isethionic and salicylic acid, as well as the salts with inorganic or organic bases, e.g. alkali or alkaline-earth
35 metals, especially sodium, potassium, calcium or magnesium hydroxides, carbonates or bicarbonates, acyclic or cyclic amines, preferably methylamine, ethylamine, diethylamine, triethylamine or piperidine.

The compounds of formula (I) may have asymmetric carbon atoms and may therefore exist either as racemic admixtures or as individual optical isomers.

Accordingly, the use as an antitumor agent of all the possible isomers and their admixtures and of both the metabolites and the pharmaceutically acceptable bio-precursors (otherwise referred to as pro-drugs) of the compounds of formula (I) are also within the scope of the present invention.

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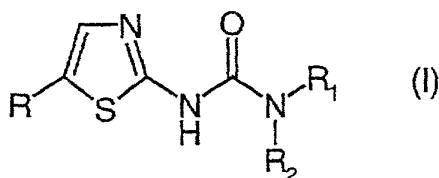
Preferred compounds of the invention are the compounds of formula (I) wherein R is a halogen atom, a straight or branched C₁-C₄ alkyl group, a phenyl or a cycloalkyl group; R₂ is hydrogen and R₁ is an optionally substituted group selected from alkyl, aryl or arylalkyl.

15

Even more preferred, within this class, are the compounds of formula (I) wherein R is bromine or chlorine, a straight or branched C₁-C₄ alkyl group, a phenyl or a cycloalkyl group; R₂ is hydrogen and R₁ is an optionally substituted aryl or an arylalkyl or heterocyclyl-alkyl group with from 1 to 4 carbon atoms within the alkyl chain.

20

Another class of preferred compounds of the invention are the compounds of formula (I)



25

wherein

R is a halogen atom or is selected from the group consisting of nitro, amino, alkylamino, hydroxyalkylamino, arylamino, C₃-C₆ cycloalkyl, straight or branched C₁-C₆ alkyl optionally substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulfonyl, alkoxycarbonyl, carboxy, aryl optionally substituted

30

by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl or carboxy, or R is an aryl group optionally substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulphonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl or carboxy;

R₁ is a straight or branched C₁-C₆ alkyl group or an aryl group, each optionally substituted as above reported for R;

R₂ is a hydrogen atom; and pharmaceutically acceptable salts thereof;

provided that:

a) when R is chlorine or bromine then R₁ is not unsubstituted C₁-C₃ alkyl, phenyl, trifluoromethylphenyl or an optionally substituted phenylcarbonyl;

b) when R is methyl then R₁ is not methyl, phenyl or 4-(5-oxazolyl)phenyl;

c) when R is nitrophenyl then R₁ is not haloalkyl.

Another class of preferred compounds of formula (I) are those wherein R is a straight or branched C₁-C₆ alkyl group and, together with the nitrogen atom to which they are bonded, R₁ and R₂ form a substituted or unsubstituted, optionally either benzocondensed or bridged 5 to 7 membered heterocycle, or 9 to 11 membered spiro-heterocycle.

Still another class of preferred compounds of formula (I) are those wherein R is a straight or branched C₁-C₆ alkyl group; R₂ is a straight or branched C₁-C₄ alkyl or C₂-C₄ alkenyl or alkynyl group and R₁ is an aryl or arylalkyl group with from 1 to 4 carbon atoms within the straight or branched alkyl chain.

Examples of preferred compounds of the invention, whenever appropriate in the form of pharmaceutically acceptable salts, e.g. hydrobromide or hydrochloride salt, are the following:

- 1) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-phenyl-urea;
- 2) N-(5-bromo-1,3-thiazol-2-yl)-N'-phenyl-urea;
- 3) N-(5-phenyl-1,3-thiazol-2-yl)-N'-phenyl-urea;
- 4) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-phenyl-urea;
- 5) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea;
- 6) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea;
- 7) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea;
- 8) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea;
- 9) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-urea;
- 10) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-urea;
- 11) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-urea;
- 12) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-urea;
- 13) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-urea;
- 14) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-urea;
- 15) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-urea;
- 16) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-urea;
- 17) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;
- 18) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;
- 19) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;

- 20) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;
- 21) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-urea;
- 5 22) N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-urea;
- 23) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-urea;
- 24) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-urea;
- 10 25) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-urea;
- 26) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-urea;
- 27) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-urea;
- 15 28) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-urea;
- 29) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-urea;
- 20 30) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-urea;
- 31) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-urea;
- 32) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-urea;
- 25 33) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-urea;
- 34) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-urea;
- 30 35) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-urea;
- 36) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-urea;
- 37) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-urea;
- 35 38) N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-urea;

- 39) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-
urea;
- 40) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-methoxy-
phenyl)-urea;
- 5 41) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-
urea;
- 42) N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-
urea;
- 43) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-
10 urea;
- 44) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-hydroxy-
phenyl)-urea;
- 45) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-
urea;
- 15 46) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-urea;
- 47) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-urea;
- 48) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-
urea;
- 49) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-
20 urea;
- 50) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-urea;
- 51) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-urea;
- 52) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-
urea;
- 25 53) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-
urea;
- 54) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-urea;
- 55) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-urea;
- 56) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-
30 urea;
- 57) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-
urea;
- 58) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-urea;
- 59) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-urea;
- 35 60) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-
urea;
- 61) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
- 62) N-(5-bromo-1,3-thiazol-2-yl)-N'-benzyl-urea;

- 63) N-(5-phenyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
64) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
65) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
66) N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
5 67) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
68) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-
urea;
69) N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
70) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
10 71) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
72) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-
urea;
73) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
74) N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
15 75) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
76) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-
urea;
77) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(benzothiophen-2-
yl)-urea;
20 78) N-(5-bromo-1,3-thiazol-2-yl)-N'-(benzothiophen-2-yl)-
urea;
79) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(benzothiophen-2-yl)-
urea; N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(
(benzothiophen-2-yl)-urea;
25 80) N-(5-isopropyl-1,3-thiazol-2-yl)-4-morpholine
carboxamide;
81) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-
methylphenyl)urea;
82) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-
30 fluorophenyl)urea;
83) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-
cyanophenyl)urea;
84) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-
cyanophenyl)urea;
35 85) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,6-
dimethylphenyl)urea;
86) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-
fluorobenzyl)urea;

- 87) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-acetylphenyl)urea;
- 88) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-acetylphenyl)urea;
- 5 89) 3-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)benzoic acid;
- 90) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-isopropylphenyl)urea;
- 91) 3-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)benzamide;
- 10 92) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methoxybenzyl)urea;
- 93) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-butylphenyl)urea;
- 15 94) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-trifluoromethylphenyl)urea;
- 95) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-bromophenyl)urea;
- 96) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-cyclohexylphenyl)urea;
- 20 97) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-phenoxyphenyl)urea;
- 98) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-benzyloxyphenyl)urea;
- 99) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-dimethylphenyl)urea;
- 25 100) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,3-dimethylphenyl)urea;
- 101) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-methoxy[1,1'-biphenyl]-4-yl)urea;
- 30 102) N-(5-isopropyl-1,3-thiazol-2-yl)-3,4-dihydro-2(1H)-isoquinoline carboxamide;
- 103) N-benzyl-N'-(5-isopropyl-1,3-thiazol-2-yl)-N-methylurea;
- 104) N-(5-isopropyl-1,3-thiazol-2-yl)-6,7-dimethoxy-3,4-dihydro-2(1H)-isoquinoline carboxamide;
- 35 105) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(3-chloro-4-methyl)-phenyl]urea;

- 106) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(3-chloro-6-methyl)phenyl]urea;
- 107) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-dimethoxyphenyl)urea;
- 5 108) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-dimethoxyphenyl)urea;
- 109) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(2-methoxy-5-chloro)phenyl]urea;
- 110) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-((2-chloro-4-methoxyphenyl)urea;
- 10 111) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-dichlorophenyl)urea;
- 112) N-[(1,1'-biphenyl)-2-yl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 15 113) N-ethyl-N'-(5-isopropyl-1,3-thiazol-2-yl)-N-phenylurea;
- 114) N-[4-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)-2-methoxyphenyl]acetamide;
- 115) 2-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)-N-phenylbenzamide;
- 20 116) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-morpholinophenyl)urea;
- 117) N-[4-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)phenyl]-N-methyl acetamide;
- 118) N-(2-{[cyclohexyl(methyl)amino]methyl}phenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 25 119) N-[3-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)-4-methoxyphenyl]acetamide;
- 120) N-(5-isopropyl-1,3-thiazol-2-yl)-4-(4-methoxyphenyl)-1-piperazine carboxamide;
- 30 121) N-(2-furylmethyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 122) N-(4-fluorophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 123) N-(2-methoxybenzyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 35 124) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[2-(1-methyl-1H-pyrrol-2-yl)ethyl]urea;

- 125) N-(3,4-dimethoxybenzyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 126) N-(5-isopropyl-1,3-thiazol-2-yl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane-8-carboxamide;
- 5 127) n-(5-isopropyl-1,3-thiazol-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxamide;
- 128) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[2-(1-piperidinyl)ethyl]urea;
- 129) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[2-(1-morpholinyl)ethyl]urea;
- 10 130) 4-(4-fluorophenyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperazine carboxamide;
- 131) N-[4-(4-chlorophenyl)-3-ethyl-5-isoxazolyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 15 132) 4-[(4-fluorophenyl)(hydroxy)methyl]-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperidine carboxamide;
- 133) N-(3-ethynylphenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 134) N-(2-methoxy-3-fluorophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 20 135) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-oxo-1-piperidinyl)urea;
- 136) N-(3-acetylaminophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 25 137) N-[3-(2-furyl)-1H-pyrazol-5-yl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 138) N-{4-[ethyl(isopropyl)amino]phenyl}-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 139) N-(1,3-benzodioxol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 30 140) 5-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)-1-phenyl-1H-pyrazole-4-carboxamide;
- 141) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-pyridinylmethyl)urea;
- 35 142) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-pyrazinyl)urea;
- 143) n-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-phenyl-1,3,4-oxadiazol-2-yl)urea;

- 144) N-(5-isopropyl-1,3-thiazol-2-yl)-4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-piperidine carboxamide;
- 145) N-(1,3-benzothiazol-6-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 5 146) N-(1,3-dimethyl-1H-pyrazol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 147) N-(3-phenyl-1-methyl-1H-pyrazol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 148) N-(5-isopropyl-1,3-thiazol-2-yl)-3-hydroxy-1-
- 10 piperidine carboxamide;
- 149) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)urea;
- 150) N-(5-isopropyl-1,3-thiazol-2-yl)-4-benzyl-1-piperazine carboxamide;
- 15 151) N-(5-isopropyl-1,3-thiazol-2-yl)-4-methyl-1-piperazine carboxamide;
- 152) 4-hydroxy-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperidine carboxamide;
- 153) N-(5-isopropyl-1,3-thiazol-2-yl)-3-
- 20 azabicyclo[3.2.2]nonane-3-carboxamide;
- 154) N-(5-isopropyl-1,3-thiazol-2-yl)-4-(4-acetylphenyl)-1-piperazine carboxamide;
- 155) 4-[bis(4-fluorophenyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperazine carboxamide;
- 25 156) N-(5-isopropyl-1,3-thiazol-2-yl)-4-oxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide;
- 157) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5,6,7,8-tetrahydro-1-naphtalenyl)urea;
- 158) N-(4-phenyl-2-thiazolyl)-N'-(5-isopropyl-1,3-thiazol-2-
- 30 yl)urea;
- 159) 4-(4-fluorobenzoyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperidine carboxamide;
- 160) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-1,3-dihydro-2-benzofuran-5-yl)urea;
- 35 161) N-(5-isopropyl-1,3-thiazol-2-yl)-4'-(2-pyrimidinyl)-1-piperazine carboxamide;
- 162) N-(5-isopropyl-1,3-thiazol-2-yl)-3-oxo-3,4-dihydro-1(2H)-quinoxaline;

- 163) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1H-indazol-6-yl)urea;
- 164) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-chlorobenzyl)urea;
- 5 165) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dichlorobenzyl)urea;
- 166) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-fluorobenzyl)urea;
- 167) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-10 dichlorobenzyl)urea;
- 168) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-difluorobenzyl)urea;
- 169) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-difluorobenzyl)urea;
- 15 170) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-2,6-difluorobenzyl)urea;
- 171) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(4-hydroxy-3-methoxy)benzyl]urea;
- 172) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-methyl-2-20 furyl)urea;
- 173) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methylsulfonylbenzyl)urea;
- 174) N-[(1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 25 175) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-chlorobenzyl)urea;
- 176) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-pyridinylmethyl)urea;
- 177) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-30 dimethoxybenzyl)urea;
- 178) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-pyridinylmethyl)urea;
- 179) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-trifluorobenzyl)urea;
- 35 180) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4,5-trimethoxybenzyl)urea;
- 181) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dimethoxybenzyl)urea;

- 182) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-dimethylaminobenzyl)urea;
- 183) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-dimethoxybenzyl)urea;
- 5 184) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(2-chloro-6-phenoxy)benzyl]urea;
- 185) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]urea;
- 186) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(3-hydroxy-4-methyl)phenyl]urea;
- 10 187) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[4-(1H-benzimidazol-2-yl)phenyl]urea;
- 188) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-phenyl-1H-pyrazol-5-yl)urea;
- 15 189) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methyl-6-quinolinyl)urea;
- 190) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[4-(cyanomethyl)phenyl]urea;
- 191) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-quinolinyl)urea;
- 20 192) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1-oxo-2,3-dihydro-1H-inden-5-yl)urea;
- 193) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-oxo-1,3-dihydro-2-benzofuran-5-yl)urea;
- 194) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)urea;
- 25 195) methyl-3-([[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl]amino)-4-methylbenzoate;
- 196) methyl-4-([[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl]amino)-3-methylbenzoate;
- 30 197) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-imidazo[1,2-a]pyridin-2-yl-phenyl)urea;
- 198) ethyl-4-([[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl]amino)benzoate;
- 199) (2R)-1-benzyl-2-([[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl]amino)propanamide;
- 35 200) 2-hydroxy-5-([[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl]benzoic acid;

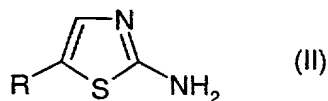
- 201) 2-chloro-5-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)benzoic acid;
202) 3-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)benzoic acid;
5 203) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-methyl-3-isoxazolyl)urea;
204) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,6-dimethoxyphenyl)urea;
205) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,3-dimethoxybenzyl)urea;
10 206) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-difluorobenzyl)urea;
207) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dimethylphenyl)urea;
15 208) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1H-benzimidazol-5-yl)urea;
209) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(R)-phenylglycinamido]urea;
210) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-phenoxyacetamido)urea;
20 211) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(S)-phenylglycinamido]urea;
212) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-{2-[(1-methyl-1H-imidazol-2-yl)methoxy]phenyl}urea;
25 213) N-(3-iodophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
214) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[3-(3-methoxy-1-propynyl)phenyl]urea;
215) N-{3-[3-(dimethylamino)-1-propynyl]phenyl}-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
30 216) N-[4-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)phenyl]methanesulfonamide;
217) 2-[3-({[(5-isopropyl-1,3-thiazol-2-ylamino]carbonyl}amino)anilino]acetamide;
218) N-[3-(3-hydroxy-1-butynyl)phenyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
35 219) N-(imidazo[1,2-a]pyridin-2-yl-methyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;

- 220) 2-{{[[[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}(2-propynyl)amino]methyl}benzenesulfonamide;
- 221) N-(1H-indol-6-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 5 222) N-[(1S)-2-hydroxy-1-phenylethyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 223) N-(1H-indol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 224) N-[(1R)-2-hydroxy-1-phenylethyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 10 225) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-butylurea;
- 226) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-benzoylurea;
- 227) N-(5-methyl-1,3-thiazol-2-yl)-N'-(2,6-dimethylphenyl)urea;
- 15 228) N-(5-methyl-1,3-thiazol-2-yl)-N'-benzylurea;
- 229) N-(5-methyl-1,3-thiazol-2-yl)-N'-butylurea;
- 230) N-(5-methyl-1,3-thiazol-2-yl)-4-morpholinecarboxamide;
- 231) N-(5-methyl-1,3-thiazol-2-yl)-N'-phenylurea;
- 232) N-(5-methyl-1,3-thiazol-2-yl)-N'-(4-methoxybenzyl)urea;
- 20 233) N-(5-methyl-1,3-thiazol-2-yl)-N'-(4-fluorophenyl)urea;
- 234) N-[(1-ethyl-2-pyrrolidinyl)methyl]-N'-(5-methyl-1,3-thiazol-2-yl)urea;
- 235) N-(5-methyl-1,3-thiazol-2-yl)-N'-(5-hydroxy-1H-pyrazol-3-yl)urea;
- 25 236) N-(5-methyl-1,3-thiazol-2-yl)-N'-(3-pyridinyl)urea;
- 237) N-(4-fluorophenyl)-N'-(5-methyl-1,3-thiazol-2-yl)urea.

The compounds of formula (I) object of the present invention and the salts thereof can be obtained, for instance, by a process comprising:

30

- a) when R₂ is a hydrogen atom
reacting a compound of formula (II)



wherein R is as defined above, with a compound of formula (III)

35

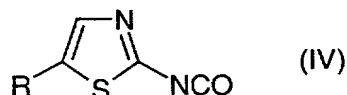


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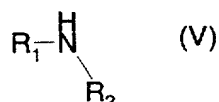
wherein R_1 is as defined above; or

b) when R_2 is a hydrogen atom or has the meanings above reported

reacting a compound of formula (IV)



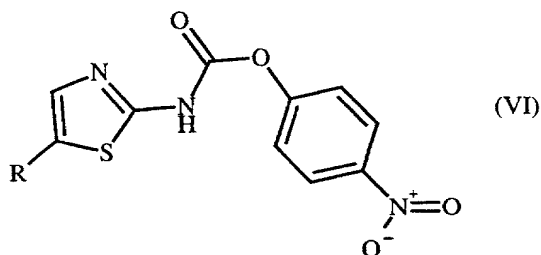
wherein R is as defined above, with a compound of formula (V)



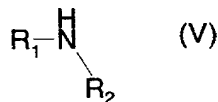
wherein R_1 and R_2 are as defined above; and, if desired, converting a 2-ureido-1,3-thiazole derivative of formula (I) into another such derivative of formula (I), and/or into a salt thereof.

The compounds of formula (I) can alternatively be obtained by a process comprising:

reacting a compound of formula (II) wherein R is as described above with 4-nitrophenyl-chloroformate, or a polymer supported form of it, thus obtaining a compound of formula (VI), or a polymer supported form of it,

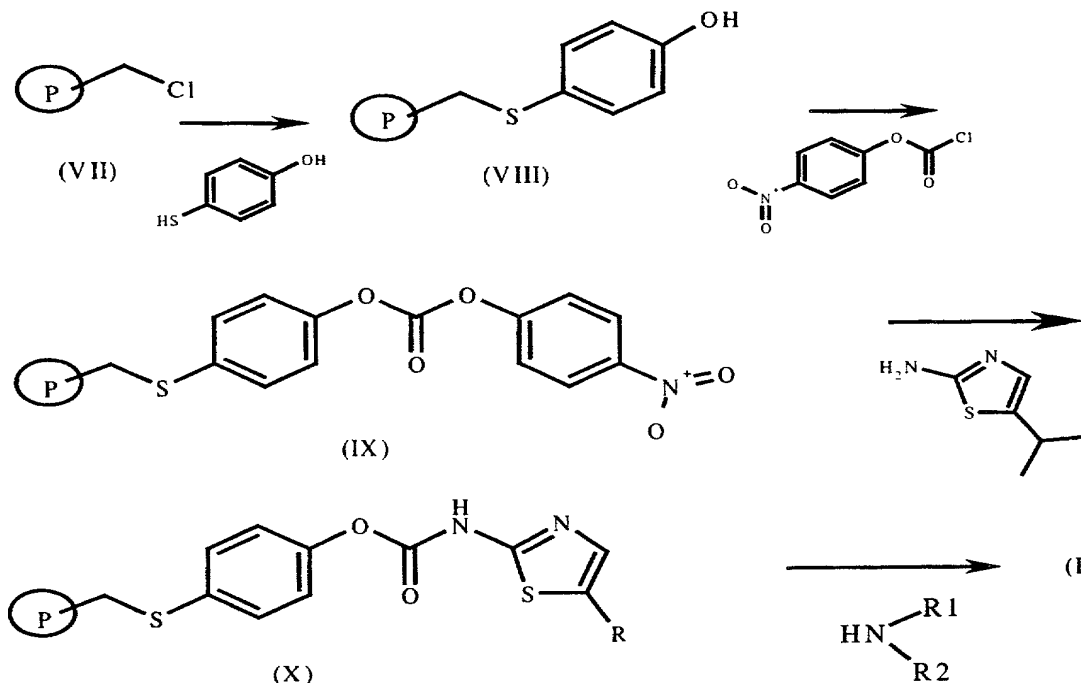


wherein R is as described above; and reacting a compound of formula (VI) with a compound of formula (V)



wherein R_1 and R_2 are as described above; and, if desired, converting a 2-ureido-1,3-thiazole derivative of formula (I), or a polymer supported form of it, into another such derivative of formula (I), and/or into a salt thereof.

More particularly, when referring to the process performed by using polymer supported species, the synthetic pathway can be summarized as follows:



5

In addition, when referring to the process performed by using polymer supported species, conventional reaction conditions are well known to the skilled man.

- 10 It is further clear to the man skilled in the art that if the compound of formula (I), prepared according to the above processes, is obtained as an admixture of isomers, their separation into the single isomers of formula (I) according to conventional techniques is still within the scope of the present invention.

15

Likewise, the conversion into the free 2-ureido-1,3-thiazole derivative (I) of a corresponding salt thereof, according to well-known procedures in the art, is still within the scope of the invention.

20

The above process-variants are analogy processes which can be carried out according to well known methods.

The reaction between a compound of formula (II) and a compound of formula (III), or the reaction between a compound of formula (IV) and a compound of formula (V), can be carried out in a suitable solvent such as, for instance, dichloromethane, chloroform, tetrahydrofuran, diethyl ether, 1,4-dioxane, acetonitrile, toluene or acetone, at a temperature ranging from room temperature to reflux for a time varying between about 1 to 96 hours.

The reaction of a compound of formula (II) to give a compound of formula (VI) is carried out with 4-nitrophenylchloroformate, or a polymer supported form of it, in the presence of a tertiary base such as, for instance, triethylamine, N-methylmorpholine, N,N-diisopropylethylamine or pyridine, in a suitable solvent such as toluene, dichloromethane, chloroform, diethylether, tetrahydrofuran, acetonitrile, dioxane or N,N-dimethylformamide, at a temperature ranging from approximately -10°C to room temperature.

The reaction between a compound of formula (VI) and a compound of formula (V) to give a compound of formula (I) can be carried out in a suitable solvent such as toluene, dichloromethane, chloroform, diethylether, tetrahydrofuran, acetonitrile, 1,4-dioxane or N,N-dimethylformamide, at a temperature ranging from about room temperature to reflux.

In the above-mentioned scheme, as far as the solid phase approach is concerned, compound (VIII) can be prepared by reacting compound (VII) with 4-mercaptophenol in the presence of a base such as potassium tert-butoxide, potassium carbonate or potassium sodium hydroxide and in a suitable solvent such as N,N-dimethylformamide at a temperature ranging from 40 to 60 °C. The reaction between compound (VIII) and p-nitrophenylchloroformate to give compound (IX) can be carried out in presence of a base such as N-methylmorpholine, triethylamine or N,N-diisopropylethylamine in a suitable solvent such as dichloromethane, chloroform, 1,4-dioxane or N,N-dimethylformamide at room temperature.

The reaction between compound (IX) and the compound of formula (II), wherein R is as described above, thus obtaining the compound of formula (X), can be carried out in a suitable solvent such as dichloromethane, chloroform, toluene or N,N-dimethylformamide at room temperature for a time varying between about 2 to 22 hours.

The reaction between the compound of formula (X), wherein R is as described above, and the compound of formula (V) wherein R₁ and R₂ are as described above, thus obtaining the compound of formula (I), can be carried out in the presence of a base such as triethylamine, N,N-diisopropylethylamine or N-methylmorpholine in a suitable solvent such as toluene, acetonitrile or N,N-dimethylformamide at a temperature ranging from room temperature to 100°C.

Also the optional conversion of a compound of formula (I) into another compound of formula (I) can be carried out according to known methods.

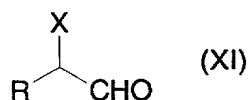
As an example, the nitro group of a compound of formula (I) may be converted into an amino group by treatment, for example, with stannous chloride in concentrated hydrochloric acid and by using, if necessary, an organic solvent such as acetic acid, 1,4-dioxane and tetrahydrofuran, at a temperature varying between room temperature and about 100°C.

Likewise, an alkylthio or an arylthio group may be converted into the corresponding alkylsulfonyl and arylsulfonyl group by reaction, for example, with m-chloroperbenzoic acid in a suitable solvent such as dichloromethane or chloroform, at a temperature varying from about -5°C and room temperature.

The optional salification of a compound of formula (I) or the conversion of a salt into the free compound as well as the separation of a mixture of isomers into the single isomers may be carried out by conventional methods.

The compounds of formula (II) and (IV) according to the above processes are known compounds or can be obtained according to known methods.

For example, a compound of formula (II) wherein R is as defined above can be obtained by reacting a compound of formula (XI)



- 5 wherein X is a bromine or chlorine atom, with thiourea in a suitable solvent such as methanol, ethanol, tetrahydrofuran, 1,4-dioxane or toluene, at a temperature varying between room temperature and reflux, for a suitable time ranging from about 1 hour to about 24 hours.
- 10 A compound of formula (IV) can be obtained, for instance, by reacting a compound of formula (II) wherein R is as defined above with bis(trichloromethyl) carbonate or trichloromethyl chloroformate in the presence, if necessary, of a tertiary base such as triethylamine, N,N-diisopropylethylamine or pyridine, in a suitable solvent
- 15 such as dichloromethane, chloroform or toluene, at a temperature ranging from about -20°C to reflux. The compounds of formula (III), (V) and (XI) are well-known commercially available compounds or, alternatively, may be
- 20 conventionally prepared according to known methods in organic chemistry.

When preparing the compounds of formula (I) according to the process object of the present invention, optional functional groups within both the starting materials or the

25 intermediates thereof, which could give rise to unwanted side reactions, need to be properly protected according to conventional techniques.

Likewise, the conversion of these latter into the free deprotected compounds may be carried out according to known

30 procedures.

Pharmacology

The compounds of formula (I) are active as cdk/cyclin inhibitors as they gave positive results when tested

35 according to the following procedure.

The compounds of formula (I) are therefore useful to restrict the unregulated proliferation of tumor cells, hence in therapy in the treatment of various tumors such as, for instance, carcinomas, e.g. mammary carcinoma, lung carcinoma, bladder carcinoma, colon carcinoma, ovary and endometrial tumors, sarcomas, e.g. soft tissue and bone sarcomas, and the hematological malignancies such as, e.g., leukemias.

In addition, the compounds of formula (I) are also useful in the treatment of other cell proliferative disorders such as psoriasis, vascular smooth cell proliferation associated with atherosclerosis and post-surgical stenosis and restenosis and in the treatment of Alzheimer's disease.

The inhibiting activity of putative cdk/cyclin inhibitors and the potency of selected compounds was determined through a method of assay based on the use of the MultiScreen-PH 96 well plate (Millipore), in which a phosphocellulose filter paper was placed at each well bottom allowing binding of positive charged substrate after a washing/filtration step.

When a radioactivity labelled phosphate moiety was transferred by the ser/threo kinase to the filter-bound histone, light emitted was measured in a scintillation counter.

The inhibition assay of cdk2/Cyclin A activity was performed according to the following protocol:

Kinase reaction: 1.5 μ M histone H1 substrate, 25 μ M ATP (0.5 μ Ci $P^{33}\gamma$ -ATP), 30 ng Cyclin A/ckd2 complex, 10 μ M inhibitor in a final volume of 100 μ l buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, 7.5 mM DTT) were added to each well of a 96 U bottom well plate. After 10 min at 37 °C incubation, reaction was stopped by 20 μ l EDTA 120 mM.

Capture: 100 μ l were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 μ l/well PBS $\text{Ca}^{++}/\text{Mg}^{++}$ free and filtered by
5 MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 μ l/well scintillant were added and ^{33}P labelled histone H1 was detected by radioactivity counting in the Top-Count
10 instrument.

Results: data were analysed and expressed as % inhibition referred to total activity of enzyme (=100%). All compounds showing inhibition ≥ 50 % were further analysed in order to study and define potency (IC_{50}) as
15 well as the kinetic-profile of inhibitor through K_i calculation.

IC_{50} determination: the protocol used was the same described above, where inhibitors were tested at concentrations ranging from 0.0045 to 10 μM . Experimental
20 data were analyzed by the computer program GraphPad Prizm.

K_i calculation: either the concentration of ATP and histone H1 substrate were varied: 4, 8, 12, 24, 48 μM for ATP (containing proportionally diluted $\text{P}^{33}\gamma\text{-ATP}$) and 0.4, 0.8, 1.2, 2.4, 4.8 μM for histone were used in absence and
25 presence of two different, properly chosen inhibitor concentrations.

Experimental data were analysed by the computer program SigmaPlot for K_i determination, using a random bireactant system equation:

$$V = \frac{V_{\max} \frac{(A)(B)}{aK_A K_B}}{1 + \frac{(A)}{K_A} + \frac{(B)}{K_B} + \frac{(A)(B)}{aK_A K_B}}$$

35 where A=ATP and B=histone H1.

Following the method above described, a representative compound of formula (I) of the invention, which is N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-dimethylphenyl)urea, showed an inhibiting activity towards the cdk2/cyclin A complex corresponding to 0.56 μ M (IC50).

In addition, the inhibiting activity of putative cdk/cyclin inhibitors and the potency of selected compounds was determined through a method of assay based on the use of a SPA (Scintillation Proximity Assay) 96 well plate assay. The assay is based on the ability of streptavidin coated SPA beads to capture a biotinylated peptide derived from a phosphorylation site of histone.

When a radioactivity labelled phosphate moiety was transferred by the ser/threo kinase to the biotinylated histone peptide, light emitted was measured in a scintillation counter.

The inhibition assay of cdk5/p25 activity was performed according to the following protocol:

Kinase reaction: 1.0 μ M biotinylated histone peptide substrate, 0.25 uCi P33g-ATP, 4 nM cdk2/p25 complex, 0-100 μ M inhibitor in a final volume of 100 μ l buffer (Hepes 20 mM pH 7.5, MgCl2 15 mM, 1 mM DTT) were added to each well of a 96 U bottom well plate. After 20 min at 37 °C incubation, the reaction was stopped by the addition of 500 ug SPA beads in phosphate-buffered saline containing 0.1% Triton X-100, 50 uM ATP and 5 mM EDTA. The beads were allowed to settle, and the radioactivity incorporated in the 33P-labelled peptide was detected in a Top Count scintillation counter.

Results: Data were analyzed and expressed as % Inhibition using the formula:

$$100 \times (1 - (\text{Unknown} - \text{Bkgd}) / (\text{Enz. Control} - \text{Bkgd}))$$

IC50 values were calculated using a variation of the four parameter logistics equation:

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$$Y = 100/[1 + 10^{((\text{LogEC50} - X) \cdot \text{Slope})}]$$

Where $X = \log(\mu\text{M})$ and $Y = \% \text{ Inhibition}$.

5 The compounds of formula (I) are therefore useful to restrict the unregulated proliferation of tumor cells, hence in therapy in the treatment of various tumors such as, for instance, carcinomas, e.g. mammary carcinoma, lung carcinoma, bladder carcinoma, colon carcinoma, ovary and
10 endometrial tumors, sarcomas, e.g. soft tissue and bone sarcomas, and the hematological malignancies such as, e.g., leukemias.

In addition, the compounds of formula (I) are also useful in the treatment of other cell proliferative disorders such
15 as psoriasis, vascular smooth cell proliferation associated with atherosclerosis and post-surgical stenosis and restenosis and in the treatment of Alzheimer's disease.

The compounds of the present invention can be administered
20 either as single agents or, alternatively, in combination with known anticancer treatments such as radiation therapy or chemotherapy regimen in combination with cytostatic or cytotoxic agents.

As an example, the above compounds can be administered in
25 combination with one or more chemotherapeutic agents such as, for instance, taxane, taxane derivatives, CPT-11, camptothecin derivatives, anthracycline glycosides, e.g. doxorubicin or epirubicin, etoposide, navelbine, vinblastine, carboplatin, cisplatin and the like,
30 optionally within liposomal formulations thereof.

The compounds of formula (I) of the present invention, suitable for administration to a mammal, e.g. to humans, can be administered by the usual routes and the dosage
35 level depends upon the age, weight, conditions of the patient and the administration route.

For example, a suitable dosage adopted for oral administration of a compound of formula (I) may range from about 10 to about 500 mg pro dose, from 1 to 5 times daily. The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally in the form of suppositories; parenterally, e.g. intramuscularly, or by intravenous and/or intrathecal and/or intraspinal injection or infusion.

The present invention also includes pharmaceutical compositions comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient (which can be a carrier or a diluent).

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, sucrose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gum, gelatine, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may be e.g. syrups, emulsions and suspensions.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

5 The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

10 The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or infusions may contain as carrier, for example, sterile
15 water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions or they may contain as a carrier propylene glycol.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa
20 butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

The following examples illustrate but do not limit the present invention.

25

Example 1

Preparation of methyl cyclopropylacetate

Cyclopropylacetic acid (1.08 g; 10.57 mmol) was dissolved in 50 ml of methanol. The solution was cooled to 0°C and 5
30 ml of sulfuric acid 96% were dropped under stirring. The solution was maintained at room temperature overnight and then poured onto ice-water, basified with 30 % ammonium hydrate and finally extracted with methylene chloride. The organic layer was dried over sodium sulfate and evaporated
35 to dryness to give 1.1 g of an oily product (90% yield) which was used as such without any further purification.

Example 2

Preparation of 2-cyclopropylethanol

- Sodium (85 mg; 0.004 mmol) was dissolved in 50 ml of methanol and 8.7 g (0.23 mol) of sodium borohydride were added. A solution of 3.7 g (0.032 mol) of methyl cyclopropylacetate, prepared according to example 1, in 20 ml of methanol was dropped to the mixture under stirring. The reaction was maintained at reflux for 6 hours, then 300 ml of brine were added and the crude extracted with methylene chloride.
- The organic layer was dried over sodium sulfate and evaporated to dryness to give 1.52 g (55% yield) of the title compound.

Example 3

- Preparation of a compound of formula (VI): 2-cyclopropylethanol**

- Oxalyl chloride (1.24 ml; 14.18 mmol) was dissolved in 10 ml of methylene chloride; after cooling to -60°C a solution of 1.02 g (11.9 mmol) of 2-cyclopropylethanol, prepared according to example 2, in 10 ml of methylene chloride was added dropwise. The mixture was maintained under stirring for 30 minutes at the same temperature, then 8.3 ml (59.5 mmol) of triethylamine were added.
- After 2 hours at 0°C water was added. The mixture was diluted with methylene chloride and washed successively with 1M hydrochloric acid, water, saturated sodium bicarbonate and finally with brine. The organic layer was dried over sodium sulfate and evaporated to dryness to give 0.31 g (30% yield) of the title compound.

Example 4**Preparation of a compound of formula (II): 2-amino-5-isopropyl-1,3-thiazole**

- 3-Methylbutanaldehyde (2 ml; 18.6 mmol) was dissolved in 15 ml of dioxane.
- A solution 2% v/v of bromine in dioxane (47.81 ml; 18.6 mmol) was dropped therein at 0°C. The mixture was maintained at room temperature under stirring for 2 hours,

- 38 -

then 2.83 g (37.2 mmol) of thiourea and 10 ml of ethanol were added. After 6 hours at room temperature the solution was evaporated to dryness, the residue was dissolved in methylene chloride and the product extracted with 1M
5 hydrochloric acid; the aqueous layer was made basic by using 30% ammonium hydrate and extracted again with methylene chloride.

The organic phase was dried over sodium sulfate and evaporated under vacuum. The residue was chromatographed on
10 a silica gel column, eluting with cyclohexane-ethylacetate to give 1.1 g (42% yield) of the title compound.

¹H-NMR (DMSO-d⁶) δ ppm: 6.6 (s, 2H, NH₂); 6.58 (s, 1H, thiazole CH); 2.9 (m, 1H, CHMe₂); 1.18 (s, 3H, MeCHMe); 1.17 (s, 3H, MeCHMe).

15 By analogous procedures the following compounds can be prepared:

2-amino-5-phenyl-1,3-thiazole; and
2-amino-5-cyclopropyl-1,3-thiazole.

Example 5

Preparation of a compound of formula (I): N-(5-bromo-1,3-thiazol-2-yl)-N'-phenyl-urea

Phenylisocyanate (1.7 ml; 15.6 mmol) was added to a
25 solution of 2-amino-5-bromo-1,3-thiazole hydrobromide (4 g; 15.6 mmol) and triethylamine (2.1 ml; 15.6 mmol) in dichloromethane (70 ml), maintained under magnetic stirring at room temperature. After about 4 days, methanol (7 ml) was added and the reaction mixture was then washed with
30 brine, dried over sodium sulfate and evaporated.

The residue was purified by chromatography on silica gel (dichloromethane and then dichloromethane/methanol=90:10) to give 1.9 g (52%) of the title compound as a colourless solid (m.p. 166-169°C/dec.).

35 ¹H-NMR (CDCl₃) δ ppm: 10.50 (bs, 1H, -NHCONHPh); 8.50 (bs, 1H, -NHCONHPh); 7.45 (d, J = 7.6 Hz, 2H, o-Ph hydrogens);

7.36 (dd, $J = 7.3$ and 7.6 Hz, 2H, *m*-Ph hydrogens); 7.29 (s, 1H, thiazole CH); 7.16 (t, $J = 7.3$ Hz, 1H, *p*-Ph hydrogens).

By analogous procedure, and by starting from the
5 corresponding isocyanate, the following compounds can be prepared:

N-(5-phenyl-1,3-thiazol-2-yl)-N'-phenyl-urea

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 10.56 (bs, 1H, -NHCONHPh); 8.99 (bs, 1H, NHCONHPh); 7.77 (s, 1H, thiazole CH); 7.6-7.0 (m, 10H, phenyl);
10

N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea

m.p. >200°C

15 $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 10.58 (bs, 1H, -NHCONHPh); 9.38 (bs, 1H NHCONHPh); 7.75 (d, 2H, H3 and H5 Ph); 7.61 (d, 2H, H2 and H6 Ph); 7.21 (s, 2H, SO_2NH_2); 7.02 (s, 1H, thiazole CH); 3.02 (m, 1H, $\text{CH}(\text{Me})_2$); 1.22 (s, 3H, MeCHMe); 1.21 (s, 3H, MeCHMe);

20 ESI(+)-MS: m/z 341 (100, $(\text{M}+\text{H})^+$).

N-benzoyl-N'-(5-isopropyl-1,3-thiazol-2-yl)urea

m.p. 217-219°C

$^1\text{H-NMR}$ (400 MHz-DMSO- d_6) δ ppm: 1.27 (d, 6H, $J=6.8$, CH_3CHCH_3); 3.11 (m, 1H, CH_3CHCH_3); 7.18 (d, 1H, $J=0.9$, H thiazole); 7.54 (m, 2H, *m*-phenyl); 7.66 (m, 1H, *p*-phenyl);
25 8.00 (m, 2H, *o*-phenyl); 11.50 (bs, 1H, NH); 11.80 (bs, 1H, NH).

ESI (+)MS: m/z 290 (70, $(\text{M}+\text{H})^+$; m/z 169 (100, $(\text{MH}-\text{C}_6\text{H}_5\text{CONH}_2)^+$);

30 N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea;

N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-urea

m.p. 149-150°C

35 $^1\text{H-NMR}$ (400 MHz-DMSO- d_6) δ ppm: 1.23 (d, 6H, $J=6.8$, CH_3CHCH_3); 3.06 (m, 1H, CH_3CHCH_3); 3.72 (s, 3H, CH_3); 7.02 (s, 1H, H thiazole); 6.57 (dd, 1H, $J=8.3$, 2.4, H-4'-phenyl);

6.93 (d, 1H, J=8.3, H-6'-phenyl); 7.18 (m, 2H, H-5', H-2'-phenyl); 8.94 (s, 1H, NH); 10.35 (bs, 1H, NH).

ESI (+)MS: m/z 292 (100, (M+H)⁺);

N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-urea

5 m.p. 190-191°C

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 7.44 (s, 1H, H thiazole);

3.72 (s, 3H, CH₃); 6.61 (dd, 1H, J=2.4, 7.8, H-4'-phenyl);

6.94 (dd, 1H, J=2.0, 7.8, H-6'-phenyl); 7.13 (dd, 1H, J=2.0,

2.0, H-2'-phenyl); 7.20 (dd, 1H, J=7.8, 7.8, H-5'-phenyl);

10 8.95 (s, 1H, NH); 10.80 (s, 1H, NH).

ESI (+)MS: m/z 328 (100, (M+H)⁺);

N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-urea;

N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-urea;

15

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-phenyl-urea

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.8,

CH₃CHCH₃); 3.07 (m, 1H, CH₃CHCH₃); 7.03 (m, 2H, H-thiazole +

H-4'-phenyl); 7.29 (m, 2H, H-5', H-3'-phenyl); 7.43 (m, 2H,

20 H-2', H-6'-phenyl); 8.91 (s, 1H, NH); 10.30 (bs, 1H, NH).

ESI(+)-MS: m/z 262 (100, (M+H)⁺);

N-(5-phenyl-1,3-thiazol-2-yl)-N'-phenyl-urea;

N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-phenyl-urea;

25 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-urea

m.p. 191-193°C

¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.16 (d, 6H, J=6.8,

CH₃CHCH₃); 3.00 (m, 1H, CH₃CHCH₃); 6.95 (d, 1H, J=1.0, H

thiazole); 7.40 (d, 2H, J=8.9 m-phenyl); 7.26 (d, 2H, J=8.9

30 o-phenyl); 9.01 (bs, 1H, NH); 10.40 (bs, 1H, NH).

ESI (+)MS: m/z 296 (100, (M+H)⁺);

N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-urea;

N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-urea;

N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-

35 urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;

N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;

N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;

N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-urea

- 5 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.8, CH₃CHCH₃); 3.07 (m, 1H, CH₃CHCH₃); 7.07 (m, 2H, H-thiazole + H-4'-phenyl); 7.31 (dd, 1H, J=7.8, 7.8, H-5'-phenyl); 7.47 (d, 1H, J=7.8 H-3'-phenyl); 8.14 (d, 1H, J=7.8, H-6'-phenyl); 8.80 (bs, 1H, NH); 11.01 (bs, 1H, NH).

- 10 ESI (+)MS: m/z 296 (100, (M+H)⁺);

N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-urea
m.p. 210-212°C

- ¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 7.29 (s, 1H, H-thiazole); 7.02 (ddd, 1H, J=1.6, 7.6, 7.6, H-4'-phenyl); 7.25 (ddd, 1H, J=1.6, 7.6, 7.6, H-5'-phenyl); 7.41 (dd, 1H, J=1.6, 7.6, H-3'-phenyl); 8.03 (dd, 1H, J=1.6, 7.6, H-6'-phenyl); 8.58 (s, 1H, NH); 11.31 (bs, 1H, NH).
- 15

ESI (+)MS: m/z 332 (100, (M+H)⁺);

N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-urea;

- 20 N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-urea;

N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-urea;

N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-urea;

- 25 N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-urea;

N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-urea;

N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-urea;

N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-

- 30 urea;

N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-urea;

N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-urea;

N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-urea;

- 35 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-urea
m.p. 184-185°C;

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.7, CH₃CHCH₃); 3.07 (m, 1H, CH₃CHCH₃); 3.85 (s, 3H, OCH₃); 6.92 (m, 1H, H-phenyl); 7.01 (m, 3H, H-phenyl + H-thiazole); 8.07 (d, 1H, J=8.3, H-6'-phenyl); 8.80 (bs, 1H, NH); 10.82 (s, 1H, NH).

5 ESI(+)-MS: m/z 292 (100, (M+H)⁺);

N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-urea
m.p. 218-220°C

¹H-NMR (300 MHz-DMSO-d₆) δ ppm: 3.79 (s, 3H, CH₃O); 6.90-7.98 (2m, 4H, phenyl); 7.36 (s, 1H, H thiazole); 8.57 (s, 1H, NH); 11.13 (bs, 1H, NH).

10 ESI (+)MS: m/z 328 (100, (M+H)⁺)

N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-urea;
N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-urea;

15

N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-urea;
N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-urea;
N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-urea;

20 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-urea

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.14 (m, 1H, CH₃CHCH₃); 7.04 (s, 1H, H-thiazole); 7.74 (d, 2H, J=9.3, H-2', H-6'-phenyl); 8.18 (d, 2H, J=9.3, H-3', H-5'-phenyl); 9.65 (bs, 1H, NH); 11 (bs, 1H, NH).

25 ESI(+)-MS: m/z 307 (100, (M+H)⁺);

N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-urea;
N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-urea;
N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-urea

30 m.p. 220-222°C

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.9, CH₃CHCH₃); 3.05 (m, 1H, CH₃CHCH₃); 7.04 (s, 1H, H thiazole); 7.56 (dd, 1H, J=8.2, 8.2, H-5'-phenyl); 7.77 (d, 1H, J=8.2, H-6'-phenyl); 7.83 (dd, 1H, J=8.2, 1.5, H-4'-phenyl); 8.58 (d, 1H, J=1.5, H-2'-phenyl); 9.45 (s, 1H, NH); 10.60 (bs, 1H, NH).

35

ESI (+)MS: m/z 307 (100, (M+H)⁺);

- N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-urea;
 N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-urea;
 N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-urea;
 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-benzyl-urea
 5 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.8, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 4.31 (d, 2H, J=6.35, CH₂); 6.96 (m, 1H, NH-CH₂); 7.27 (m, 5H, phenyl).
 ESI (+)MS: m/z 276 (100, (M+H)⁺);
 N-(5-bromo-1,3-thiazol-2-yl)-N'-benzyl-urea;
 10 N-(5-phenyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
 N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
 N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
 N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
 15 N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
 N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
 N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
 N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
 20 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
 N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
 N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
 N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(benzothiophen-2-yl)-
 25 urea;
 N-(5-bromo-1,3-thiazol-2-yl)-N'-(benzothiophen-2-yl)-urea;
 N-(5-phenyl-1,3-thiazol-2-yl)-N'-(benzothiophen-2-yl)-urea;
 and
 N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(benzothiophen-2-yl)-
 30 urea.

EXAMPLE 6

Preparation of a compound of formula (VI): 4-nitrophenyl-5-isopropyl-1,3-thiazol-2-ylcarbamate

- 35 To a solution of 4 g (28.13 mmol) of 5-isopropyl-2-amino-1,3-thiazole in 30 ml of anhydrous dichloromethane 5.7 g (28.13 mmol) of 4-nitrophenyl chloroformate were added dropwise at 0°C under nitrogen. Then 2.3 ml of pyridine

were added. The mixture was maintained at room temperature under stirring overnight and then filtered, giving 6.96 g (80% yield) of the title compound as a white solid.

m.p. 157-159°C

- 5 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.06 (m, 1H, CH₃CHCH₃); 7.05 (s, 1H, H thiazole); 6.91 (d, 2H, J=9.2, H-3',5'-phenyl); 8.10 (d, 2H, J=9.2, H-2',6'-phenyl); 11.00 (bs, 1H, NH).
EI-MS: m/z 307 (0.5, M⁺); m/z 168 ((CH₃)₂-CH-thiazole-NCO)⁺;
10 m/z 153 (100, (CH₃-CH-thiazole-NCO)⁺); m/z 139 (45, (OH-C₆H₄-NO₂)⁺).

EXAMPLE 7

Preparation of a compound of formula (I):N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-iodophenyl)urea

- 15 1 g (3.25 mmol) of 4-nitrophenyl-5-isopropyl-1,3-thiazol-2-ylcarbamate and 0.39 ml (3.25 mmol) of 3-iodoaniline were suspended under argon in 25 ml of acetonitrile. After 2 hours at 70°C the resulting solution was cooled, giving
20 rise 0.923 g of the title compound, recrystallized from a mixture of diethylether/pentane 1/1.

m.p. 160-162°C

- ¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.05 (m, 1H, CH₃CHCH₃); 7.03 (d, 1H, J=0.8, H thiazole); 7.07 (t, 1H, J=8.0, H-5'-phenyl); 7.35 (m, 2H, H-4',6'-phenyl); 8.00 (t, 1H, J=1.8, 1.8, H-2'-phenyl); 9.06 (bs, 1H, NH); 10.50 (bs, 1H, NH).
ESI(+)-MS: m/z 388 (100, (M+H)⁺).

- 30 By analogous procedure but employing 2-[(2-propynylamino)methyl]benzenesulfonamide, 2-[[[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}(2-propynyl)amino]methyl]benzenesulfonamide can be prepared.
m.p. 90-92°C

- 35 ¹H-NMR (400 MHz-DMSO) δ ppm: 1.19 (d, 6H, J=6.8, CH₃CHCH₃); 2.93 (m, 1H, CH≡C-); 3.13 (m, 1H, CH₃CHCH₃); 4.18, 5.08 (2m,

4H, $\text{CH}_2\text{Ph} + \text{CH}_2\text{C}\equiv\text{C}$); 6.89 (m, 1H, H-thiazole); 7.22 (m, 1H, H-3'-phenyl); 7.41, 7.53 (2m, 2H, H-5', H-4'-phenyl); 7.86 (m, 1H, H-6'-phenyl); 11.90 (bs, 1H, NH).

ESI(+)-MS: m/z 415 (100, $(\text{M}+\text{Na})^+$); m/z 393 (50, $(\text{M}+\text{H})^+$).

- 5 By analogous procedure but employing 1H-benzimidazol-6-amine, N-(1H-benzimidazol-5-yl)N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be obtained.

¹H- NMR (400 MHz-DMSO- d_6) δ ppm: 1.27 (d, 6H, $\text{J}=6.8$, CH_3CHCH_3); 3.09 (m, 1H, CH_3CHCH_3); 7.01 (s, 1H, H-thiazole); 7.13 (d, 1H, H-6'-benzimidazole); 7.49 (d, 1H, H-7'-benzimidazole); 7.81 (s, 1H, H-4'-benzimidazole); 8.03 (s, 1H, H-2'-benzimidazole).

ESI(+)-MS: m/z 302 (100, $(\text{M}+\text{H})^+$).

- 15 By analogous procedure but employing 1H-indole-6-amine, N-(1H-indol-6-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared.

¹H- NMR (400 MHz-DMSO- d_6) δ ppm: 1.24 (d, 6H, $\text{J}=6.8$, CH_3CHCH_3); 3.06 (m, 1H, CH_3CHCH_3); 7.03 (bs, 1H, H-thiazole); 6.33 (m, 1H, H-3'-indole); 6.84 (d, 1H, $\text{J}=8.3$, H-5'-indole); 7.23 (t, 1H, $\text{J}=2.4$, 2.4, H-2'-indole); 7.42 (d, 1H, $\text{J}=8.3$, H-4'-indole); 7.77 (s, 1H, H-7'-indole); 8.82 (s, 1H, NH); 10.18 (bs, 1H, NH); 10.95 (s, 1H, NH-indole).

ESI(+)-MS: m/z 301 (100, $(\text{M}+\text{H})^+$).

- 25 By analogous procedure but employing 1H-indole-5-amine, N-(1H-indol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared.

¹H- NMR (400 MHz-DMSO- d_6) δ ppm: 1.24 (d, 6H, $\text{J}=6.8$, CH_3CHCH_3); 3.06 (m, 1H, CH_3CHCH_3); 7.02 (s, 1H, H-thiazole); 6.35 (m, 1H, H-3'-indole); 7.05 (dd, 1H, $\text{J}=2.0$, $\text{J}=8.5$, H-6'-indole); 7.30 (m, 2H, H-2', H-7'-indole); 7.67 (d, 1H, $\text{J}=2.0$, H-4'-indole); 8.68 (s, 1H, NH); 10.15 (s, 1H, NH); 10.98 (s, 1H, NH-indole).

ESI(+)-MS: m/z 301 (100, $(\text{M}+\text{H})^+$).

By analogous procedure but employing imidazo[1,2-a]pyridin-2-ylmethanamide, N-(imidazo[1,2-a]pyridin-2-yl-methyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared.

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.8, CH₃CHCH₃); 3.04 (m, 1H, CH₃CHCH₃); 4.40 (d, 2H, J=5.6, CH₂); 6.96 (d, 1H, J=1.2, H thiazole); 6.84 (dt, 1H, J=2.2, 6.8, H-6'-imidazopyridine); 7.20 (m, 1H, H-5'-imidazopyridine); 7.47 (m, 1H, H-7'-imidazopyridine); 7.78 (s, 1H, H-3'-imidazopyridine); 8.49 (m, 1H, H-4'-imidazopyridine); 7.01 (t, 1H, J=5.4, NH-CH₂); 10.23 (bs, 1H, NH-CO).

ESI(+)-MS: m/z 316 (100, (M+H)⁺); m/z 338 (85, (M+Na)⁺).

By analogous procedure but employing 1-methyl-2-[(2-aminophenoxy)methyl]1H-imidazole, N-(5-isopropyl-1,3-thiazol-2-yl)-N'-{2-[(1-methyl-1H-imidazol-2-yl)methoxy]phenyl}urea can be prepared.

¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.05 (m, 1H, CH₃CHCH₃); 3.70 (s, 3H, N-CH₃); 5.21 (s, 2H, CH₂); 6.92 (bs, 1H, H thiazole); 6.90-8.20 (m, 6H, imidazole+phenyl); 8.10 (bs, 1H, NH); 10.96 (s, 1H, NH).

ESI(+)-MS: m/z 372 (95, (M+H)⁺); m/z 410 (100, (M+K)⁺).

By analogous procedure but employing 2-(2-aminophenoxy)acetamide, N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-phenoxyacetamido)urea can be prepared.

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=7.0, CH₃CHCH₃); 3.07 (m, 1H, CH₃CHCH₃); 4.50 (s, 2H, CH₂); 7.05 (d, 1H, J=1.0, H thiazole); 6.50-7.00 (m, 3H, phenyl); 8.10 (m, 1H, phenyl), 7.55 (s, 2H, NH₂), 8.67 (bs, 1H, NH); 10.86 (s, 1H, NH).

ESI(+)-MS: m/z 335 (50, (M+H)⁺); m/z 373 (100, (M+K)⁺).

By analogous procedure but employing (2S)-2-amino-2-phenylethanamide, N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(S)-phenylglycinamido]urea can be prepared.

¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.19 (d, 6H, J=6.8, CH₃CHCH₃); 3.01 (m, 1H, CH₃CHCH₃); 5.26 (d, 1H, J=7.7 CH); 6.95 (s, 1H, H-thiazole); 7.20-7.60 (m, 6H, NH-CH+phenyl); 7.20-7-80 (s, 2H, NH₂), 10.26 (bs, 1H, NH).

ESI(+)-MS: m/z 319 (25, (M+H)⁺); m/z 357 (100, (M+K)⁺);

By analogous procedure but employing (2R)-2-amino-2-phenylethanamide, N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(R)-phenylglycinamido]urea can be prepared.

- 5 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.19 (d, 6H, J=7.0, CH₃CHCH₃); 3.01 (m, 1H, CH₃CHCH₃); 5.26 (d, 1H, J=7.6 CH); 6.95 (d, 1H, J=1.3, H thiazole); 7.20-7.50 (m, 6H, NH-CH+phenyl); 7.21-7.79 (s, 2H, NH₂), 10.20 (bs, 1H, NH).

ESI(+)-MS: m/z 319 (100, (M+H)⁺); m/z 357 (65, (M+K)⁺).

- 10 By analogous procedure but employing 2-aminophenol, N-(2-hydroxyphenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared.

m.p. 204-206°C

- ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.06 (m, 1H, CH₃CHCH₃); 7.02 (s, 1H, H-thiazole); 6.74 (m, 1H, H-5'-phenyl); 6.82 (m, 2H, H-3', H-4'-phenyl); 7.98 (d, 1H, J=7.6, H-6'-phenyl); 8.60 (bs, 1H, NH); 10.0 (bs, 1H, NH); 10.80 (bs, 1H, OH).

ESI(+)-MS: m/z 278 (100, (M+H)⁺).

- 20 By analogous procedure but employing 3-aminophenol, N-(3-hydroxyphenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared.

m.p. 185-187°C

- ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.05 (m, 1H, CH₃CHCH₃); 7.03 (m, 3H, H-thiazole + H-2', H-5'-phenyl); 6.39 (d, 2H, J=8.0, H-4'-phenyl); 6.77 (d, 2H, J=8.0, H-6'-phenyl); 8.81 (s, 1H, NH); 9.37 (s, 1H, NH).

ESI(+)-MS: m/z 278 (100, (M+H)⁺).

- By analogous procedure but employing 4-aminophenol, N-(4-hydroxyphenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared.

m.p. 130-132°C

- ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.05 (m, 1H, CH₃CHCH₃); 7.00 (s, 1H, H-thiazole); 6.68 (d, 2H, J=8.8, H-3', H-5'-phenyl); 7.21 (d, 2H, J=8.8, H-2', H-6'-phenyl); 8.60 (s, 1H, NH); 9.14 (s, 1H, NH); 10.18 (bs, 1H, OH).

ESI(+)-MS: m/z 278 (100, (M+H)⁺).

By analogous procedure but employing (2R)-2-amino-2-phenyl-1-ethanol, N-[(1S)-2-hydroxy-1-phenylethyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared.

5 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.20 (d, 6H, J=7.0, CH₃CHCH₃); 3.01 (m, 1H, CH₃CHCH₃); 3.60 (m, 2H, CH₂); 4.73 (m, 1H, CH); 5.00 (t, 1H, J=5.1, 5.1, OH); 6.95 (d, 1H, J=1.1, H thiazole); 7.10-7.40 (m, 6H, NH-CH+phenyl), 10.15 (s, 1H, NH).

10 ESI(+)-MS: m/z 306 (100, (M+H)⁺).

By analogous procedure but employing (2S)-2-amino-2-phenyl-1-ethanol, N-[(1R)-2-hydroxy-1-phenylethyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared.

15 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.19 (d, 6H, J=6.9, CH₃CHCH₃); 3.01 (m, 1H, CH₃CHCH₃); 3.59 (m, 2H, CH₂); 4.73 (m, 1H, CH); 5.02 (t, 1H, J=5.1, 5.1, OH); 6.95 (d, 1H, J=0.7, H thiazole); 7.20-7.40 (m, 6H, NH-CH+phenyl), 10.17 (s, 1H, NH).

ESI(+)-MS: m/z 306 (100, (M+H)⁺).

20

EXAMPLE 8

Preparation of a compound of formula (I): N-[3-(3-hydroxy-1-butyryl)phenyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea

To a solution of 0.2 g (0.56 mmol) of N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-iodophenyl)urea in 3 ml of anhydrous N,N-dimethylformamide 0.6 ml of tetramethylguanidine, 0.088 ml (1.126 mmol) of D,L-1-butyryl-3-ol, 19 mg (0.027 mmol) of bis(triphenylphosphine)palladium(II)dihydrochloride and 5.8 mg (0.03 mmol) of rameous iodide under argon were added
25 successively. After 5 hours water was added and the mixture extracted with ethylacetate. The organic layer was washed with brine, dried over sodium sulfate and evaporated, giving 0.116 g of the title compound as a yellowish solid.
30 m.p. 71-73°C

35 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.9, CH₃CHCH₃); 3.06 (m, 1H, CH₃CHCH₃); 1.37 (d, 3H, J=6.6, CH₃); 4.57 (m, 1H, CH); 5.43 (d, 1H, J=5.1, OH); 7.03 (s, 1H,

H thiazole); 7.02 (d, 1H, J=8.0, H-4'-phenyl); 7.27 (t, 1H, J=8.0, 8.0, H-5'-phenyl); 7.34 (d, 1H, J=8.0, H-6'-phenyl); 7.65 (s, 1H, H-2'-phenyl); 8.02 (s, 1H, NH); 10.40 (bs, 1H, NH).

5 ESI(+)-MS: m/z 330 (100, (M+H)⁺).

By analogous procedure and by starting from N,N-dimethyl-2-propenyl-1-amine, N-{3-[3-(dimethylamino)-1-propynyl]phenyl}-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared;

10 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.05 (m, 1H, CH₃CHCH₃); 2.23 (s, 6H, N(CH₃)₂); 3.44 (s, 2H, CH₂); 7.03 (s, 1H, H-thiazole); 7.05 (d, 1H, J=7.8, H-4'-phenyl); 7.27 (t, 1H, J=7.8, 7.8, H-5'-phenyl); 7.36 (d, 1H, J=7.8, H-6'-phenyl); 7.64 (s, 1H, H-2'-phenyl); 9.04
15 (bs, 1H, NH); 10.45 (bs, 1H, NH).

ESI(+)-MS: m/z 343 (100, (M+H)⁺).

By analogous procedure and by starting from 3-methoxy-1-propyne, N-[3-(3-methoxy-1-propynyl)phenyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared;

20 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.05 (m, 1H, CH₃CHCH₃); 3.32 (s, 3H, CH₃); 4.31 (s, 2H, CH₂); 7.03 (s, 1H, H-thiazole); 7.08 (d, 1H, J=8.3, H-4'-phenyl); 7.29 (t, 1H, J=8.3, 8.3, H-5'-phenyl); 7.39 (d, 1H, J=8.3, H-6'-phenyl); 7.67 (s, 1H, H-2'-phenyl); 9.03 (s,
25 1H, NH); 10.40 (bs, 1H, NH).

ESI(+)-MS: m/z 330 (100, (M+H)⁺).

EXAMPLE 9

30 **Preparation of a compound of formula (I): N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-aminophenyl)urea**

A mixture of 1.55 g (5.05 mmol) of (5-isopropyl-1,3-thiazol-2-yl)-N'-(3-nitrophenyl)urea prepared as described in example 5 and 0.98 g ((17.7 mmol) of iron dust with 2.02
35 ml (35.35 mmol) of glacial acetic acid in 50 ml of ethanol was stirred at reflux under argon atmosphere. After 5 hours 1.5 l of water was added and the product extracted with

ethylacetate. The organic layer was washed with brine, dried over sodium sulfate and evaporated. The residue was finally purified by chromatography on a silica gel column (chloroform/methanol 47/3) giving 0.84 g of the title compound as a white solid.

m.p. 113-115°C

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.05 (m, 1H, CH₃CHCH₃); 5.07 (s, 2H, NH₂); 7.02 (s, 1H, H-thiazole); 6.20 (dd, 1H, J=2.0, 7.8, H-4'-phenyl); 6.52 (dd, 1H, J=1.5, 8.3, H-6'-phenyl); 6.76 (bs, 1H, H-2'-phenyl); 6.89 (t, 1H, J=8.3, 8.3, H-5'-phenyl); 8.61 (s, 1H, NH); 10.13 (bs, 1H, NH).

ESI(+)-MS: m/z 277 (100, (M+H)⁺).

By analogous procedure and by starting respectively from N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-nitrophenyl)urea and N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-nitrophenyl)urea, the following compounds can be prepared:

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-aminophenyl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-aminophenyl)urea;

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.22 (d, 6H, J=6.8, CH₃CHCH₃); 3.04 (m, 1H, CH₃CHCH₃); 4.83 (s, 2H, NH₂); 6.99 (s, 1H, H-thiazole); 6.50 (d, 2H, J=8.7, H-3', H-5'-phenyl); 7.05 (d, 2H, J=8.7, H-2', H-6'-phenyl); 8.42 (s, 1H, NH); 10.09 (bs, 1H, NH).

ESI(+)-MS: m/z 277 (100, (M+H)⁺).

Again by analogous procedure, and by starting respectively from 6-nitro-1H-indole and from 6-nitro-1H-benzimidazole, 1H-indol-6-amine and 1H-benzimidazol-6-amine can be prepared.

EXAMPLE 10

Preparation of a compound of formula (I): N-[4-({[(5-isopropyl-1,3-thiazol-2-yl)amino]phenyl}methanesulfonamide
0.2 g (0.724 mmol) of N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-aminophenyl)urea were dissolved in 10 ml of absolute

ethanol and 0.2 g (1.95mmol) of potassium hydrogen carbonate and 124.3 mg (1.0855 mmol) of methanesulfonylchloride were added successively. The mixture was maintained at 80°C under argon for 7 hours and

then evaporated. The residue was partitioned between water and dichloromethane. The organic layer was then dried over sodium sulfate and afforded, after concentration and cooling, 104 mg of the title compound as a white solid.

m.p. 246-248°C

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.06 (m, 1H, CH₃CHCH₃); 2.97 (s, 3H, CH₃); 7.03 (s, 1H, H-thiazole); 6.84 (d, 1H, J=6.8, H-6'-phenyl); 7.19 (m, 2H, H-4', H-5'-phenyl); 7.39 (s, 1H, H-2'-phenyl); 9.00 (s, 1H, NH); 9.72 (bs, 1H, NH); 10.18 (bs, 1H, NHSO₂).

ESI(+)-MS: m/z 355 (100, (M+H)⁺).

EXAMPLE 11

Preparation of a compound of formula (I):

2-[3-({[5-isopropyl-1,3-thiazol-2-

yl)amino]carbonyl)amino)anilino]acetamide

To a solution of 0.2 g (0.724 mmol) of N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-aminophenyl)urea in 2 ml of N,N-dimethylformamide, 100 mg (0.724 mmol) of 2-bromoacetamide and 108.6 mg (1.95 mmol) of potassium hydrogencarbonate were added successively. The mixture was maintained 8 hours at 40°C under argon, then poured into water and extracted with dichloromethane. The organic layer was then washed with brine, dried over sodium sulfate and concentrated to give, after cooling, 160 mg of the title compound.

m.p. 133-135°C

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.06 (m, 1H, CH₃CHCH₃); 3.54 (d, 2H, J=5.4, CH₂); 7.02 (s, 1H, H-thiazole); 5.88 (m, 1H, NH-CH₂); 6.21 (d, 1H, J=7.8, H-4'-phenyl); 6.65 (d, 1H, J=7.8, H-6'-phenyl); 6.69 (s, 1H, H-2'-phenyl); 6.98 (t, 1H, J=7.8, H-5'-phenyl); 8.71 (s, 1H, NH); 10.11 (s, 1H, NH); 7.08, 7.29 (s, 2H, NH₂).

ESI(+)-MS: m/z 334 (100, (M+H)⁺).

EXAMPLE 12

Preparation of (2R)-2-amino-2-phenylethanamide

3.025 g (15 mmol) of (2R)-2-amino-2-phenylethanoate hydrochloride were suspended in 45 ml of dioxane and 45 ml of aqueous ammonium hydrate were added. After 8 hours at room temperature under stirring the solvent was evaporated and the residue redissolved with chloroform and washed with water. The organic layer was concentrated to afford 1.7 g of the title compound as a white solid.

By analogous procedure and by starting from (2S)-2-amino-2-phenylethanoate, (2S)-2-amino-2-phenylethanamide can be prepared.

EXAMPLE 13

Preparation of 1-methyl-2-[(2-nitrophenoxy)methyl]-1H-imidazole

A solution of 1.92 g (11.97 mmol) of o-nitrophenol sodium salt, 3.8 g (35.9 mmol) of sodium carbonate, 2 g (11.97 mmol) of 1-methyl-2-chloromethylimidazole hydrochloride in 30 ml of N,N-dimethylformamide were heated at 50°C for 2 hours. The mixture was then poured into water and extracted with ethylacetate. The organic layer was washed with brine, dried over sodium sulfate and evaporated, affording 1.17 g of the title compound, recrystallized from diethylether.

m.p. 172-174°C

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 3.67 (s, 3H, CH₃); 5.34 (s, 2H, OCH₂); 6.86 (s, 1H, H-4-imidazole); 7.13 (m, 1H, H-6-phenyl); 7.19 (s, 1H, H-5-imidazole); 7.60 (m, 1H, H-3-phenyl).

ESI(+)-MS: m/z 234 (100, (M+H)⁺).

By analogous procedure and by starting from 2-chloroacetamide, 2-(2-nitrophenoxy)acetamide can be prepared.

m.p. 190-192°C

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 4.65 (s, 2H, CH₂); 7.14 (ddd, 1H, J=1.0, 7.5, 7.9, H-4); 7.22 (dd, 1H, J=1.0, 8.7); H-6); 7.32, 7.47 (2bs, 2H, CONH₂); 7.64 (ddd, J=1.5, 7.5, 8.7, H-5); 7.90 (dd, 1H, J=1.5, 7.9, H-3).

5 ESI(+)MS: m/z 197 (100, (M+H)⁺).

EXAMPLE 14

Preparation of 1-methyl-2-[(2-aminophenoxy)methyl]-1H-imidazole

10 A solution of 1.13 g of 1-methyl-2-[(2-nitrophenoxy)methyl]-1H-imidazole in 70 ml of methanol with 0.14 g of palladium on charcoal 10 % was hydrogenated at 50 psi for 6 hours at room temperature. The catalyst was then
15 separated by filtration and the solvent evaporated. The residue was finally purified by chromatography on a silica gel column (eluent: chloroform-methanol 48/2) giving rise 0.856 g of the title compound as a red oil.

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 3.72 (s, 3H, CH₃); 3.80 (bs, 2H, NH₂); 5.15 (s, 2H, H-3 + H-4-phenyl); 6.81 (m, 1H, H-5-phenyl); 6.90 (s, 1H, H-4-imidazole); 7.02 (m, 2H, H-6-phenyl + H-5-imidazole).

ESI(+)MS: m/z 204 (100, (M+H)⁺).

By analogous procedure and by starting from 2-(2-nitrophenoxy)acetamide, 2-(2-aminophenoxy)acetamide can be
25 prepared.

m.p. 114-116°C

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 4.30 (s, 2H, CH₂CO); 5.03 (s, 2H, NH₂); 6.45 (m, 1H, H-5); 6.61 (m, 1H, H-3); 6.67 (m, 1H, H-4); 6.72 (m, 1H, H-6); 7.45 (s, 1H, CONH); 7.73 (s, 1H, CONH₂).

ESI(+)MS: m/z 167 (100, (M+H)⁺).

EXAMPLE 15

Preparation of 2-(imidazo[1,2-a]pyridin-2-ylmethyl)-1H-isoindole-1,3(2H)-dione

35

4 g (0.024 mol) of 2-(chloromethyl)imidazo[1,2-a]pyridine were dissolved in 140 ml of N,N-dimethylformamide and 4.81 g (0.026 mol) of potassium ftalimide were added portionwise. The mixture was heated at 60°C for 20 hours.

5 The precipitate was filtered, washed with water, diethylether and finally tetrahydrofuran, affording 4.8 g of the title compound.

m.p. 230-232°C

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 4.88 (s, 2H, CH₂); 6.82 (m, 1H, H-6-imidazopyridine); 7.17 (m, 1H, H-5-imidazopyridine); 7.44 (m, 1H, H-7-imidazopyridine); 7.88 (m, 4H, H-phenyl); 8.42 (m, 1H, H-4-imidazopyridine).

ESI(+)MS: m/z 278 (100, (M+H)⁺).

15 EXAMPLE 16

Preparation of imidazo[1,2-a]pyridin-2-ylmethanamine

A solution of 1.37 g (4.94 mmol) of 2-(imidazo[1,2-a]pyridin-2-ylmethyl)-1H-isoindole-1,3(2H)-dione in 14 ml of hydrazine hydrate 98 % and 1 ml of ethanol. Was stirred at room temperature for an hour. The mixture was then poured into 25 ml of sodium hydroxide 35 % and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and evaporated to give 0.426 g of the title compound crystallized from diethylether.

25 m.p. 91-93°C

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 1.98 (bs, 2H, NH₂); 3.78 (s, 2H, CH₂); 6.80 (m, 1H, H-6); 7.15 (m, 1H, H-5); 7.41 (m, 1H, H-7); 7.73 (s, 1H, H-3); 8.46 (m, 1H, H-4).

ESI(+)MS: m/z 148 (100, (M+H)⁺).

30 EXAMPLE 17

Preparation of the polymer supported compound (VIII)

A solution of 8.72 g (69.1 mmol) of 4-mercaptophenol in 20 ml of dry N,N-dimethylformamide was added dropwise to a solution of 7.76 g (69.1 mmol) of potassium t-butoxyde in 120 ml of the same solvent, under argon atmosphere, at 5°C, over a period of 20 minutes. 25 g (19.75 mmol) of the

Merrifield resin (VII) (Novabiochem loading 0.79 mmol/g) was added to the solution and the temperature was kept to 60°C. The mixture was gently stirred at 60°C for 18 hours and at 22°C for 24 hours. The resin was then filtered, washed with N,N-dimethylformamide, dichloromethane, methanol and evaporated. The loading of 4-mercaptophenol on the resin was calculated from the percentage of sulfur determined via microanalysis: S 2.64 %; loading 0.755 mmol S/g. The presence of OH group was confirmed via DRIFTS (broad strong band 3180-3520 nm).

EXAMPLE 18

Preparation of the polymer supported compound (IX)

7.98 g (39.6 mmol) of 4-nitrophenylchloroformate and 4.35 ml (39.6 mmol) of N-methylmorpholine were added to 24 g (19.8 mmol) of the polymer supported compound (VIII) swelled in 200 ml of dichloromethane under argon atmosphere. The mixture was stirred at 22°C for 22 hours. The obtained compound (IX) was filtered, washed with dichloromethane, methanol and evaporated under vacuum. The loading of 4-nitro-phenylchloroformate on the resin was calculated from the percentage of sulfur determined via microanalysis: S 2.34 %; loading 0.731 mmol S/g. The disappearance of the OH band (broad strong band 3400 nm) and the appearance of carbonate group were monitored via DRIFTS (strong band 1785 nm).

EXAMPLE 19

Preparation of a polymer supported compounds (X)

A solution of 2-amino-5-isopropyl-1,3-thiazole (39.6 mmol) in 12.5 ml of dichloromethane was added to the polymer supported compound (IX) (19.8 mmol) swelled in 200 ml of dichloromethane under argon atmosphere. The mixture was stirred at 22°C for 22 hours. The obtained compound (X) was filtered, washed with dichloromethane, methanol and evaporated under vacuum. The loading of 2 amino-5-isopropyl-1,3-thiazole on the resin was calculated from the percentage of sulfur determined via microanalysis: S 4.21

%; loading 0.724 mmol S/g. The presence of carbamate group was confirmed via DRIFTS (strong band 1742 nm).

EXAMPLE 20

5 Preparation via parallel synthesis of the compounds of formula (I)

The amines (V) (0.236 mmol) and N,N-diisopropylethylamine (0.236 mmol) were added to the polymer supported compounds (X) (0.118 mmol) swelled in 3 ml of toluene in the Argonaut
10 Quest 210 apparatus vessels. 128 mg (4 eq) of N,N-diisopropylethylamine resin bounded (PS-DIEA loading 3.68 mmol/g) was used whenever the amines were in the salified form. The reactions were stirred for 22 hours at 60°C, then the reaction mixtures were filtered and the resin
15 washed with dichloromethane. The liquid phase, recovered in Climax test tubes, was evaporated under nitrogen flux at 35°C using Liebisch Termochem Metal-block thermostat. The obtained crude products were triturated with diethylether-dichloromethane and the resulting solids were filtered on
20 frit equipped syringes (Alltech extract-clean filter tubes 1.5 ml, Alltech Teflon frits for 1.5 ml tubes). The products were finally dried under vacuum.

Employing this procedure and using the suitable amine the following compounds can be prepared:

- 25 N-(5-isopropyl-1,3-thiazol-2-yl)-4-morpholine carboxamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methylphenyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-fluorophenyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-cyanophenyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-cyanophenyl)urea;
30 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,6-dimethylphenyl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-fluorobenzyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-acetylphenyl)urea

- ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=7.0,
35 CH₃CHCH₃); 3.06 (m, 1H, CH₃CHCH₃); 2.55 (s, 3H, COCH₃); 7.32 (t, 1H, J=7.6, H-5'-phenyl); 7.44 (t, 1H, J=7.9, H-5'-phenyl); 7.5-7.8 (m, 2H, H-4', H-6'-phenyl); 8.08 (s, 1H,

H-2'-phenyl); 7.04 (s, 1H, H-thiazole); 9.2 (bs, 1H, CONH-phenyl); 10.5 (bs, 1H, NHCONHPh);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-acetylphenyl)urea;
 5 3-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)benzoic acid;
 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-isopropylphenyl)urea;
 3-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)benzamide

10 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.8, CH₃CHCH₃); 3.05 (ept, 1H, J=6.8, CH₃CHCH₃); 7.32 (t, 1H, J=7.6, H-5'-phenyl); 7.35 (t, 1H, J=1.5, H-2'-phenyl); 7.49 (d, 1H, J=7.6, H-6'-phenyl); 7.62 (dd, 1H, J=7.6, 1.5, H-4'-phenyl); 7.04 (s, 1H, H-thiazole); 9.64 (s, 1H, CONH-phenyl); 10.36 (s, 1H, NHCONHPh);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methoxybenzyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-butylphenyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-
20 trifluoromethylphenyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-bromophenyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-
cyclohexylphenyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-phenoxyphenyl)urea

25 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=7.0,
CH₃CHCH₃); 3.05 (m, 1H, CH₃CHCH₃); 6.96 (m, 4H, H-3', H-5'-
phenyl, H-2', H-6'-phenoxy); 7.02 (s, 1H, H-thiazole); 7.08
(m, 1H, H-4'-phenoxy); 7.35 (m, 2H, H-3', H-5'-phenoxy); 7.47
(m, 2H, H-2', H-6'-phenyl); 8.95 (bs, 1H, CONH-phenyl); 10.3
30 (bs, 1H, NHCONH);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-benzyloxyphenyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-dimethylphenyl)urea
¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8,
CH₃CHCH₃); 3.05 (ept, 1H, J=6.8, CH₃CHCH₃); 2.22 (s, 6H, 2
35 CH₃); 6.65-7.06 (m, 3H, H-phenyl); 7.02 (s, 1H, H-thiazole);
6.71 (s, 1H, H-phenyl); 6.72 (s, 1H, H-phenyl); 8.75 (bs,
1H, CONH-phenyl); 10.3 (bs, 1H, NHCONH).

Variable	Mean	SD	Min	Max
Age	35.2	12.5	18	65
Gender	Male	10	0	20
Education	High School	15	0	30
Marital Status	Married	12	0	25
Income	\$25,000	\$15,000	\$5,000	\$50,000
Health Status	Good	18	0	35
Exercise Frequency	Weekly	10	0	20
Stress Level	Low	12	0	25
Sleep Quality	Good	15	0	30
Dietary Habits	Healthy	10	0	20
Alcohol Consumption	Low	5	0	15
Tobacco Use	None	2	0	10
Family Size	2	1	0	5
Home Ownership	Owned	15	0	30
Commute Time	30 min	15 min	10 min	60 min
Work Satisfaction	High	10	0	20
Life Satisfaction	High	15	0	30
Overall Health Score	75	10	50	100

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,3-dimethylphenyl)urea;

- ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.4, CH₃CHCH₃); 2.99 (ept, 1H, J=6.8, CH₃CHCH₃); 2.7 (t 2H, J=5.5, CH₂NCH₂CH₂); 3.68 (t, 2H, J=5.5, CH₂NCH₂CH₂); 3.69 (s, 3H, OCH₃); 3.71 (s, 3H, OCH₃); 4.55 (s, 2H, CH₂NCH₂CH₂); 6.97 (s, 1H, H-thiazole); 6.71 (s, 1H, H-phenyl); 6.72 (s, 1H, H-phenyl); 10.7 (bs, 1H, NH).

20 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(3-chloro-4-methyl)-
phenyl]urea;

25 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-dimethoxyphenyl)urea

- N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-dimethoxyphenyl)urea

- 35 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=7.0, CH₃CHCH₃); 3.05 (ept, 1H, J=7.0, CH₃CHCH₃); 3.7 (s 3H, OCH₃); 3.73 (s, 3H, OCH₃); 7.02 (s, 1H, H-thiazole); 6.8-7.2 (m,

3H, H-phenyl); 8.76 (s, 1H, NHCONHPh); 10.2 (s, 1H, NHCONHPh);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(2-methoxy-5-chloro)phenyl]urea:

5 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-((2-chloro-4-methoxyphenyl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-dichlorophenyl)urea;

N-[(1,1'-biphenyl)-2-yl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;

N-ethyl-N'-(5-isopropyl-1,3-thiazol-2-yl)-N-phenylurea;

N-[4-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)-2-methoxyphenyl]acetamide;

2-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)-N-
15 phenylbenzamide;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-morpholinophenyl)urea;

N-[4-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)phenyl]-N-methyl acetamide

20 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.22 (d, 6H, J=6.6, CH₃CHCH₃); 3.08 (m, 1H, CH₃CHCH₃); 1.73 (s, 3H, NCOCH₃); 7.03 (s, 1H, H-thiazole); 3.09 (s, 3H, CH₃NCOCH₃); 7.23 (d, 2H, J=8.1, H-6', H-2'-phenyl); 7.51 (d, 2H, J=8.1, H-5', H-3'-phenyl); 9.1 (bs, 1H, NHCONHPh); 10.4 (bs, 1H, NHCONHPh);

25 N-(2-{[cyclohexyl(methyl)amino]methyl}phenyl)-N'-(5-
isopropyl-1,3-thiazol-2-yl)urea;

N-[3-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)-4-methoxyphenyl]acetamide;

N-(5-isopropyl-1,3-thiazol-2-yl)-4-(4-methoxyphenyl)-1-piperazine carboxamide;

N-(2-furylmethyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.8, CH₃CHCH₃); 2.99 (ept, 1H, J=6.8, CH₃CHCH₃); 4.32 (d, 2H, J=5.6, NHCH₂); 6.26 (d, 1H, J=3, H-5'-furyl); 6.4 (d, 1H, J=3, H-4'-furyl); 6.98 (s, 1H, H-thiazole); 6.93 (t, 1H, NHCH₂); 7.59 (s, 1H, H-3'-furyl); 10.19 (bs, 1H, NHCO).

ESI(+)-MS: m/z 266 (100, $(M+H)^+$);

- N-(4-fluorophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
N-(2-methoxybenzyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[2-(1-methyl-1H-pyrrol-2-yl)ethyl]urea;
- 5 N-(3,4-dimethoxybenzyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea
- ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=7.0, CH₃CHCH₃); 3.01 (ept, 1H, J=7.0, CH₃CHCH₃); 3.69 (s, 3H, OCH₃); 3.72 (s, 3H, OCH₃); 4.22 (d, 2H, J=5.0, NHCH₂Ph); 6.8-6.9 (m, 3H, H-phenyl); 6.96 (s, 1H, H-thiazole);
- 10 N-(5-isopropyl-1,3-thiazol-2-yl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane-8-carboxamide
- ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.03 (ept, 1H, J=6.8, CH₃CHCH₃); 1.62 (d, 2H, J=13.6, H-3'eq, H-5'eq-piperidine); 2.4 (td, 2H, J=13.6, 5.1, H-3'ax, H-5'ax-piperidine); 3.46 (bt, 2H, J=10.4, H-6'ax, H-2'ax-piperidine); 4.14 (bd, 2H, J=10.4, H-6'eq, H-2'eq-piperidine); 4.58 (s, 2H, CONHCH₂NPh); 6.6-6.7 (m, 3H, H-2', H-6', H-4'-phenyl); 7.14 (t, 2H, J=7.5, H-3', H-5'-phenyl);
- 20 6.98 (bs, 1H, H-thiazole); 8.75 (bs, 1H, CONHCH₂NPh); 10.85 (bs, 1H, thiazole-NHCON);
- N-(5-isopropyl-1,3-thiazol-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxamide;
- N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[2-(1-piperidinyl)ethyl]urea;
- 25 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[2-(1-morpholinyl)ethyl]urea;
- 4-(4-fluorophenyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperazine carboxamide;
- 30 N-[4-(4-chlorophenyl)-3-ethyl-5-isoxazolyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 4-[(4-fluorophenyl)(hydroxy)methyl]-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperidine carboxamide;
- N-(3-ethynylphenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 35 N-(2-methoxy-3-fluorophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-oxo-1-piperidinyl)urea;

N-(3-acetylaminophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;

5 N-[3-(2-furyl)-1H-pyrazol-5-yl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;

N-{4-[ethyl(isopropyl)amino]phenyl}-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;

10 N-(1,3-benzodioxol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;

5-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)-1-phenyl-1H-pyrazole-4-carboxamide;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-pyridinylmethyl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-pyrazinyl)urea;

15 n-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-phenyl-1,3,4-oxadiazol-2-yl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-piperidine carboxamide

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=7.0, CH₃CHCH₃); 3.01 (ept, 1H, J=7.0, CH₃CHCH₃); 1.69 (bd, 2H, J=9.8, H-3'eq, H-5'eq-piperidine); 2.21 (m, 2H, H-3'ax, H-5'ax-piperidine); 3.46 (bt, 2H, J=12.4, H-2'ax, H-6'ax-piperidine); 4.14 (m, 3H, H-2'eq, H-6'eq, H-4'ax-piperidine); &.9-7.2 (m, 4H, aromatics); 6.98 (s, 1H, H-thiazole); 25 10.8 (bs, 2H, NHCONH);

N-(1,3-benzothiazol-6-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.8, CH₃CHCH₃); 3.05 (ept, 1H, J=6.8, CH₃CHCH₃); 7.5 (dd, 1H, J=8.8, 1.9, H-5'-benzothiazole); 7.98 (d, 1H, J=8.8, H-4'-benzothiazole); 8.38 (d, 1H, J=1.9, H-7'-benzothiazole); 9.22 (s, 2H, H-2'-benzothiazole + NHCONHPh); 7.04 (s, 1H, H-thiazole); 10.41 (s, 1H, NHCONHPh);

35 N-(1,3-dimethyl-1H-pyrazol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;

N-(3-phenyl-1-methyl-1H-pyrazol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;

- N-(5-isopropyl-1,3-thiazol-2-yl)-3-hydroxy-1-piperidine carboxamide;
- N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)urea;
- 5 N-(5-isopropyl-1,3-thiazol-2-yl)-4-benzyl-1-piperazine carboxamide;
- N-(5-isopropyl-1,3-thiazol-2-yl)-4-methyl-1-piperazine carboxamide;
- 4-hydroxy-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperidine
- 10 carboxamide;
- N-(5-isopropyl-1,3-thiazol-2-yl)-3-azabicyclo[3.2.2]nonane-3-carboxamide;
- N-(5-isopropyl-1,3-thiazol-2-yl)-4-(4-acetylphenyl)-1-piperazine carboxamide
- 15 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=7.0, CH₃CHCH₃); 2.99 (ept, 1H, J=7.0, CH₃CHCH₃); 2.44 (s, 3H, CH₃COPh); 3.29 (bt, 4H, CH₂-2', 6'-piperazine); 3.63 (bt, 4H, CH₂-3', 5'-piperazine); 6.97 (d, 2H, J=9.2, H-3', 5'-phenyl); 7.8 (d, 2H, J=9.2, H-2', 6'-phenyl); 6.97 (s, 1H,
- 20 H-thiazole); 10.95 (bs, 1H, NHCON);
- 4-[bis(4-fluorophenyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperazine carboxamide;
- N-(5-isopropyl-1,3-thiazol-2-yl)-4-oxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide;
- 25 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5,6,7,8-tetrahydro-1-naphtalenyl)urea;
- N-(4-phenyl-2-thiazolyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 4-(4-fluorobenzoyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-
- 30 piperidine carboxamide;
- N-(5-isopropyl-1,3-thiazol-2-yl)-N'-1,3-dihydro-2-benzofuran-5-yl)urea;
- N-(5-isopropyl-1,3-thiazol-2-yl)-4'-(2-pyrimidinyl)-1-piperazine carboxamide;
- 35 N-(5-isopropyl-1,3-thiazol-2-yl)-3-oxo-3,4-dihydro-1(2H)-quinoxaline;
- N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1H-indazol-6-yl)urea

¹H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.25 (d, 6H, J=6.8, CH₃CHCH₃); 3.07 (m, 1H, CH₃CHCH₃); 6.94 (d, 1H, J=8.4, H-5'-indazole); 7.65 (d, 1H, J=8.4, H-4'-indazole); 7.94 (m, 2H, H-3', H-7'-indazole); 7.04 (s, 1H, H-thiazole); 9.12 (bs, 1H, CONH-indazole); 10.30 (bs, 1H, NH-thiazole); 12.87 (bs, 1H, NH-indazole).

ESI(+)-MS: m/z 302 (100, (M+H)⁺);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-chlorobenzyl)urea

¹H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.9, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 4.38 (d, 2H, J=5.9, CH₂); 7.3-7.44 (m, 4H, phenyl); 6.97 (d, 1H, J=0.9, H-thiazole); 7.10 (bs, 1H, NHCH₂); 10.32 (bs, 1H, NH-thiazole).

ESI(+)-MS: m/z 310 (100, (M+H)⁺);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dichlorobenzyl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-fluorobenzyl)urea

¹H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.8, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 4.32 (d, 2H, J=6.1, CH₂); 6.97 (d, 1H, J=0.9, H-thiazole); 7.0-7.4 (m, 5H, phenyl + NHCH₂); 10.30 (bs, 1H, NH-thiazole).

ESI(+)-MS: m/z 294 (100, (M+H)⁺);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-dichlorobenzyl)urea

¹H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.7, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 4.30 (d, 2H, J=6.1, CH₂); 7.28 (dd, 1H, J=2.0, 8.2, H-6'-phenyl); 7.52 (d, 1H, J=2.0, H-2'-phenyl); 7.58 (d, 1H, J=8.2, H-5'-phenyl); 6.97 (d, 1H, J=0.9, H-thiazole); 7.12 (bs, 1H, NHCH₂); 10.41 (bs, 1H, NH-thiazole).

ESI(+)-MS: m/z 143 (100, isopropylaminothiazole+H)⁺; m/z 344 (65, (M+H)⁺);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-difluorobenzyl)urea

¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.7, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 4.30 (d, 2H, J=6.0, CH₂); 6.97 (d, 1H, J=0.9, H-thiazole); 7.0-7.4 (m, 4H, phenyl + NHCH₂); 10.20 (bs, 1H, NH-thiazole).

ESI(+)-MS: m/z 312 (100, (M+H)⁺);

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ESI(+)-MS: m/z 336 (100, $(M+H)^+$);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-pyridinylmethyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-trifluorobenzyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4,5-trimethoxybenzyl)urea

- 5 ¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.8, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 4.24 (d, 2H, J=5.9, CH₂); 3.60, 3.65 (3s, 9H, 3 OCH₃); 6.60 (s, 2H, phenyl); 6.97 (s, 1H, H-thiazole); 6.99 (bs, 1H, NHCH₂); 10.20 (bs, 1H, NH-thiazole).
- 10 ESI(+)-MS: m/z 366 (100, (M+H)⁺); m/z 181 (100, (CH₃O)₃-C₇H₆⁺);
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dimethoxybenzyl)urea
¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.8, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 4.24 (d, 2H, J=5.9, CH₂); 3.70, 3.78 (2s, 6H, 2 OCH₃); 6.48 (dd, 1H, H-5'-phenyl); 6.52 (d, 1H, H-3'-phenyl); 7.05 (d, 1H, H-6'-phenyl); 6.97 (s, 1H, H-thiazole); 6.80 (bs, 1H, NHCH₂); 10.10 (bs, 1H, NH-thiazole).
- 15 ESI(+)-MS: m/z 336 (100, (M+H)⁺);
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-dimethylaminobenzyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-dimethoxybenzyl)urea;
- 20 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(2-chloro-6-phenoxy)benzyl]urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(1R, 2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(3-hydroxy-4-methyl)phenyl]urea;
- 25 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[4-(1H-benzimidazol-2-yl)phenyl]urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-phenyl-1H-pyrazol-5-yl)urea;
- 30 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methyl-6-quinolinyl)urea

¹H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.25 (d, 6H, J=6.8, CH₃CHCH₃); 3.07 (m, 1H, CH₃CHCH₃); 2.61 (s, 3H, CH₃); 7.05 (s, 1H, H-thiazole); 7.36 (d, 1H, J=8.4, H-3'-quinoline); 7.65 (dd, 1H, J=2.0, 9.0, H-7'-quinoline); 7.85 (d, 1H, J=9.0, H-8'-quinoline); 8.14 (m, 2H, H-4', H-5'-quinoline); 9.22 (bs, 1H, NHCONH-quinoline); 10.40 (bs, 1H, NH-thiazole).

ESI(+)MS: m/z 185 (100, (MH-(CH₃)₂-CH-amino-thiazole)⁺); 327 (75, (M+H)⁺);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[4-

10 (cyanomethyl)phenyl]urea

¹H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.9, CH₃CHCH₃); 3.05 (m, 1H, CH₃CHCH₃); 7.03 (s, 1H, H-thiazole); 3.94 (s, 2H, CH₂); 7.27 (d, 2H, H-3', H-5'-phenyl); 7.48 (d, 2H, J=8.5, H-2', H-6'-phenyl); 9.01 (bs, 1H, NH-phenyl); 10.30 (bs, 1H, NH-thiazole).

ESI(+)MS: m/z 301 (100, (M+H)⁺);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-quinolinyl)urea

¹H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.27 (d, 6H, J=6.8, CH₃CHCH₃); 3.13 (m, 1H, CH₃CHCH₃); 7.17 (s, 1H, H-thiazole); 20 7.44 (m, 1H, H-3'-quinoline); 7.50 (m, 1H, H-6'-quinoline); 7.75 (m, 1H, H-7'-quinoline); 7.82 (m, 1H, H-8'-quinoline); 7.90 (m, 1H, H-5'-quinoline); 8.34 (m, 1H, H-4'-quinoline); 10.45 (bs, 1H, NHCONH-quinoline); 13.02 (bs, 1H, NHCON).

ESI(+)MS: m/z 313 (100, (M+H)⁺).

25 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1-oxo-2,3-dihydro-1H-inden-5-yl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-oxo-1,3-dihydro-2-benzofuran-5-yl)urea

30 ¹H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.8, CH₃CHCH₃); 3.06 (m, 1H, CH₃CHCH₃); 7.04 (s, 1H, H-thiazole); 5.35 (s, 1H, CH₂); 7.58 (d, 1H, J=8.4, H-5'-phenyl); 7.71 (d, 1H, J=8.4, H-6'-phenyl); 8.08 (s, 1H, H-2'-phenyl); 9.34 (bs, 1H, NHCONHPh); 10.50 (bs, 1H, NHCON).

35 ESI(+)MS: m/z 318 (100, (M+H)⁺);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)urea;

methyl-3-(([(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl)amino)-4-methylbenzoate

5 ¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.25 (d, 6H, J=6.8, CH₃CHCH₃); 3.10 (m, 1H, CH₃CHCH₃); 2.30 (s, 3H, CH₃-phenyl); 3.80 (s, 3H, CH₃O); 7.05 (s, 1H, H-thiazole); 7.30 (d, 1H, H-5'-phenyl); 7.58 (dd, 1H, H-6'-phenyl); 8.55 (m, 2H, H-2'-phenyl + NHPh); 10.80 (bs, 1H, NH-thiazole).

10 ESI(+)MS: m/z 334 (100, (M+H)⁺);

methyl-4-(([(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl)amino)-3-methylbenzoate

15 ¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 2.25 (s, 3H, CH₃-phenyl); 3.83 (s, 3H, CH₃O); 7.03 (s, 1H, H-thiazole); 7.30 (d, 1H, H-3'-phenyl); 7.53 (dd, 1H, H-4'-phenyl); 8.50 (m, 2H, H-6'-phenyl + NHPh); 10.70 (bs, 1H, NH-thiazole).

ESI(+)MS: m/z 334 (100, (M+H)⁺);

20

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-imidazo[1,2-a]pyridin-2-yl-phenyl)urea

25 ¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.8, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 7.03 (s, 1H, H-thiazole); 6.84, 7.20 (2m, 2H, H-5', H-6' imidazopyridine); 7.50, 7.90 (2m, 5H, H-2', H-3', H-5', H-6'-phenyl + H-7' imidazopyridine); 8.30 (s, 1H, H-3'-imidazopyridine); 8.50 (d, 1H, H-4'-imidazopyridine); 9.00 (bs, 1H, NHCONHPh); 10.30 (bs, 1H, NHCON).

30 ESI(+)MS: m/z 236 (100, (MH-(CH₃)₂-CH-amino-thiazole)⁺); m/z 378 (85, (M+H)⁺);

ethyl-4-(([(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl)amino)benzoate

35 ¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.20 (d, 6H, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 7.00 (s, 1H, H-thiazole); 1.15 (t, 3H,

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CH₃); 3.58 (s, 2H, CH₂-phenyl); 4.06 (q, 2H, CH₂O); 7.16, 7.38 (2d, 4H, phenyl); 8.90 (bs, 1H, NHCONHPh); 10.30 (bs, 1H, NHCON).

ESI(+)-MS: m/z 348 (100, (M+H)⁺);

5

(2R)-1-benzyl-2-(([(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl)amino)propanamide;
2-hydroxy-5-(((5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl)benzoic acid

10

2-chloro-5-(((5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl)amino)benzoic acid;

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.8, CH₃CHCH₃); 3.04 (m, 1H, CH₃CHCH₃); 7.02 (s, 1H, H-thiazole); 7.35 (d, 1H, J=8.8, H-5'-phenyl); 7.55 (dd, 1H, H-6'-phenyl); 7.88 (bs, 1H, H-2'-phenyl); 9.75 (bs, 1H, NHCONHPh); 11.00 (bs, 1H, NHCON).

15

ESI(+)-MS: m/z 340 (100, (M+H)⁺);

20

3-(((5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl)amino)benzoic acid

¹H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.8, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 7.04 (s, 1H, H-thiazole); 7.40 (dd, 1H, J=7.9, H-5'-phenyl); 7.58, 7.63 (2d, 2H, J=7.9, H-4', H-6'-phenyl); 8.13 (s, 1H, H-2'-phenyl); 9.28 (s, 1H, NHCONHPh); 10.50 (bs, 1H, NHCON).

25

ESI(+)-MS: m/z 306 (100, (M+H)⁺);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-methyl-3-isoxazolyl)urea;

30

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,6-dimethoxyphenyl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,3-dimethoxybenzyl)urea

¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.8, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 4.32 (d, 2H, J=6.1, CH₂); 3.72, 3.75 (2s, 6H, 2 OCH₃); 6.8-7.0 (m, 3H, phenyl); 6.97

35

(s, 1H, H-thiazole); 6.90 (bs, 1H, NHCH_2); 10.20 (bs, 1H, NH-thiazole).

ESI (+)-MS: m/z 336 (100, $(M+H)^+$);

- 5 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-difluorobenzyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dimethylphenyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-butylurea
- 10 ¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.20 (d, 6H, CH₃CHCH₃); 3.00 (m, 1H, CH₃CHCH₃); 0.85 (t, 3H, CH₃); 1.20-1.40 (m, 4H, CH₂-CH₂); 3.10 (m, 2H, CH₂-NH); 6.94 (d, 1H, J=1.0, H-thiazole); 6.49 (t, 1H, NHCH₂); 10.5 (bs, 1H, NH-thiazole).
ESI(+)-MS: m/z 242 (100, (M+H)⁺);
- 15 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-benzoylurea;
N-(5-methyl-1,3-thiazol-2-yl)-N'-(2,6-dimethylphenyl)urea;
N-(5-methyl-1,3-thiazol-2-yl)-N'-benzylurea;
N-(5-methyl-1,3-thiazol-2-yl)-N'-butylurea;
N-(5-methyl-1,3-thiazol-2-yl)-4-morpholinecarboxamide;
- 20 N-(5-methyl-1,3-thiazol-2-yl)-N'-phenylurea;
N-(5-methyl-1,3-thiazol-2-yl)-N'-(4-methoxybenzyl)urea;
N-(5-methyl-1,3-thiazol-2-yl)-N'-(4-fluorophenyl)urea;
N-[(1-ethyl-2-pyrrolidinyl)methyl]-N'-(5-methyl-1,3-thiazol-2-yl)urea;
- 25 N-(5-methyl-1,3-thiazol-2-yl)-N'-(5-hydroxy-1H-pyrazol-3-yl)urea;
N-(5-methyl-1,3-thiazol-2-yl)-N'-(3-pyridinyl)urea;
N-(4-fluorophenyl)-N'-(5-methyl-1,3-thiazol-2-yl)urea.

30

All compounds were characterized by mass spectrometry (MS). LC-MS confirmed that in each case the principle component had a molecular ion corresponding to the expected product. The compounds showed an HPLC area % ranging from 70 to 100.

- 35 HPLC analysis:

Instrument: Beckman System Gold Cromatographer (127 Solvent module, 168 Detector, 507e Autosampler)

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Mobile A: H₂O/CH₃CN (90/10) + 0.1 % TFA.

Mobile B: H₂O/CH₃CN (10/90) + 0.075 % TFA.

Flow rate: 1.5 ml/min.

Sample volume: 20 cml.

- 5 Column: Supelco [™], Discovery RP Amide C16, 5μm, (50×4.6)mm

Temp: 25°C.

Gradient:

Time (min)	% A	% B
0	0	100
6.5	0	100
7	100	0
10	100	0

- 10 Detection: diode array UV 254 nm.

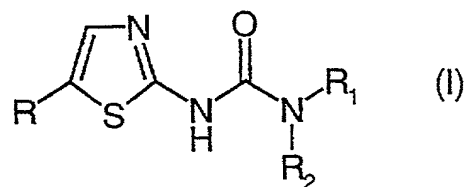
All the compounds were analyzed by MS spectrometry (ESI) using a LCQ Finnigan Mass Spectrometer.

37 randomly chosen compounds were analyzed by H¹-NMR.

The spectra were run on a Varian XL 400 Spectrometer.

CLAIMS

1. The use of a compound which is a 2-ureido-1,3-thiazole derivatives of formula (I)



5 wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

- 10 i) straight or branched C₁-C₆ alkyl;
ii) C₃-C₆ cycloalkyl;
iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R₁ is an optionally further substituted group selected from:

- 15 i) straight or branched C₁-C₆ alkyl;
ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;
iii) aryl or arylcarbonyl;
iv) arylalkyl with from 1 to 6 carbon atoms within the
20 straight or branched alkyl chain;

R₂ is hydrogen, a straight or branched C₁-C₄ alkyl or C₂-C₄ alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

25 R₁ and R₂ form a substituted or unsubstituted group selected from:

- i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or
ii) a 9 to 11 membered spiro-heterocyclic compound;
or a pharmaceutically acceptable salt thereof; in the
30 manufacture of a medicament for treating cell proliferative disorders associated with an altered cell dependent kinase activity.

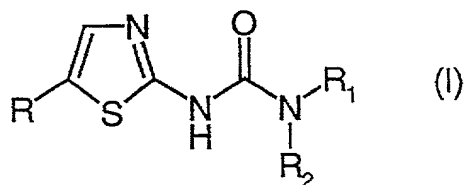
2. Use according to claim 1 wherein the said cell proliferative disorder is selected from the group consisting of cancer, Alzheimer's disease, viral infections, auto-immune diseases or neurodegenerative disorders.

3. Use according to claim 2 wherein the cancer is selected from the group consisting of carcinoma, squamous cell carcinoma, hematopoietic tumors of myeloid or lymphoid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratocanthoma, thyroid follicular cancer and Kaposi's sarcoma.

4. Use according to claim 1 wherein the cell proliferative disorder is selected from the group consisting of benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

5. Use according to any one of the preceding claims wherein the medicament enables tumor angiogenesis and metastasis inhibition.

6. A compound which is a 2-ureido-1,3-thiazole derivative of formula (I)



wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

- i) straight or branched C₁-C₆ alkyl;
- 5 ii) C₁-C₆ cycloalkyl;
- iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R₁ is an optionally further substituted group selected from:

- 10 i) straight or branched C₁-C₆ alkyl;
- ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;
- iii) aryl or arylcarbonyl;
- iv) arylalkyl with from 1 to 6 carbon atoms within the
- 15 straight or branched alkyl chain;

R₂ is hydrogen, a straight or branched C₁-C₄ alkyl or C₂-C₄ alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

R₁ and R₂ form a substituted or unsubstituted group selected from:

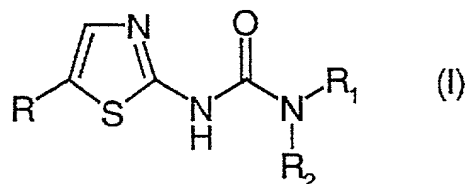
- i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or
- ii) a 9 to 11 membered spiro-heterocyclic compound; or a pharmaceutically acceptable salt thereof;

25 for use as a medicament; provided that:

- a) when R is a chlorine atom and R₂ is hydrogen, then R₁ is not methyl, phenyl or trifluoromethylphenyl; and
- b) when R is methyl and R₂ is hydrogen, then R₁ is not 4-(5-oxazolyl)phenyl.

30

7. A compound which is a 2-amino-1,3-thiazole derivative of formula (I)



wherein

i) straight or branched C₁-C₆ alkyl;

iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

10 i) straight or branched C₁-C₆ alkyl;

ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;

iii) aryl or arylcarbonyl;

iv) arylalkyl with from 1 to 6 carbon atoms within the
15 straight or branched alkyl chain;

R₂ is hydrogen, a straight or branched C₁-C₄ alkyl or C₂-C₄ alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

R₁ and R₂ form a substituted or unsubstituted group selected
20 from:

i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or

ii) a 9 to 11 membered spiro-heterocyclic compound; or a pharmaceutically acceptable salt thereof; provided that:

25 a) when R is chlorine or bromine and R₂ is hydrogen, then R₁ is not unsubstituted C₁-C₃ alkyl, phenyl, trifluoromethylphenyl or an optionally substituted phenylcarbonyl;

b) when R is methyl and R₂ is hydrogen, then R₁ is not
30 methyl, phenyl or 4-(5-oxazolyl)phenyl;

c) when R is nitrophenyl and R₂ is hydrogen, then R₁ is not haloalkyl;

d) when R is bromine or chlorine, then R₁ and R₂ are not both methyl groups.

35

8. A compound of formula (I) according to claim 7 wherein R is a halogen atom, a straight or branched C₁-C₄ alkyl group, a phenyl or a cycloalkyl group; R₁ is hydrogen and R₂

is an optionally substituted group selected from alkyl, aryl or arylalkyl.

9. A compound of formula (I) according to claim 8 wherein
5 R is bromine or chlorine, a straight or branched C₁-C₄ alkyl group, a phenyl or a cycloalkyl group; R₂ is hydrogen and R₁ is an optionally substituted aryl or an arylalkyl or heterocyclyl-alkyl group with from 1 to 4 carbon atoms within the alkyl chain.
- 10
10. A compound of formula (I) according to claim 7 wherein
R is a halogen atom or is selected from the group consisting of nitro, amino, alkylamino, hydroxyalkylamino, arylamino, C₃-C₆ cycloalkyl, straight
15 or branched C₁-C₆ alkyl optionally substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulfonyl, alkoxycarbonyl, carboxy, aryl optionally substituted by one or more hydroxy, halogen, nitro, alkoxy,
20 aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy, or R is an aryl group optionally substituted by one or more hydroxy, halogen,
25 nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulphonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy;
30 R₁ is a straight or branched C₁-C₆ alkyl group or an aryl group, each optionally substituted as above reported for R;
R₂ is a hydrogen atom; and pharmaceutically acceptable
35 salts thereof;
provided that:

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- a) when R is chlorine or bromine then R_1 is not unsubstituted C_1-C_3 alkyl, phenyl, trifluoromethylphenyl or an optionally substituted phenylcarbonyl;
- b) when R is methyl then R_1 is not methyl, phenyl or 4-(5-oxazolyl)phenyl;
- c) when R is nitrophenyl then R_1 is not haloalkyl.

11. A compound of formula (I) according to claim 7 wherein R is a straight or branched C_1-C_6 alkyl group and, together with the nitrogen atom to which they are bonded, R_1 and R_2 form a substituted or unsubstituted, optionally benzocondensed or bridged 5 to 7 membered heterocycle, or a 9 to 11 membered spiro-heterocycle.

12. A compound of formula (I) according to claim 7 wherein R is a straight or branched C_1-C_6 alkyl group; R_2 is a straight or branched C_1-C_4 alkyl or C_2-C_4 alkenyl or alkynyl group and R_1 is an aryl or arylalkyl group with from 1 to 4 carbon atoms within the straight or branched alkyl chain.

13. A compound of formula (I) according to any one of the preceding claims, whenever appropriate in the form of pharmaceutically acceptable salts, selected from the group consisting of:

- 1) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-phenyl-urea;
- 2) N-(5-bromo-1,3-thiazol-2-yl)-N'-phenyl-urea;
- 3) N-(5-phenyl-1,3-thiazol-2-yl)-N'-phenyl-urea;
- 4) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-phenyl-urea;
- 5) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea;
- 6) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea;
- 7) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea;
- 8) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea;
- 9) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-urea;

- 10) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-
urea;
- 11) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-
urea;
- 5 12) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-methoxy-
phenyl)-urea;
- 13) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-
urea;
- 14) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-urea;
- 10 15) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-
urea;
- 16) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-chloro-
phenyl)-urea;
- 17) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-
15 urea;
- 18) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;
- 19) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-
urea;
- 20) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-chloro-
20 phenyl)-urea;
- 21) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-
urea;
- 22) N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-urea;
- 23) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-
25 urea;
- 24) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-chloro-
phenyl)-urea;
- 25) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-
urea;
- 30 26) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-
urea;
- 27) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-
urea;
- 28) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-methoxy-
35 phenyl)-urea;
- 29) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-
urea;

- 30) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-
urea;
- 31) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-
urea;
- 5 32) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-hydroxy-
phenyl)-urea;
- 33) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-
urea;
- 34) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-
10 urea;
- 35) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-
urea;
- 36) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-hydroxy-
phenyl)-urea;
- 15 37) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-
urea;
- 38) N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-
urea;
- 39) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-
20 urea;
- 40) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-methoxy-
phenyl)-urea;
- 41) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-
urea;
- 25 42) N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-
urea;
- 43) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-
urea;
- 44) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-hydroxy-
30 phenyl)-urea;
- 45) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-
urea;
- 46) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-urea;
- 47) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-urea;
- 35 48) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-
urea;
- 49) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-
urea;

- 50) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-urea;
51) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-urea;
52) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-
urea;
5 53) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-
urea;
54) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-urea;
55) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-urea;
56) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-
10 urea;
57) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-
urea;
58) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-urea;
59) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-urea;
15 60) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-
urea;
61) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
62) N-(5-bromo-1,3-thiazol-2-yl)-N'-benzyl-urea;
63) N-(5-phenyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
20 64) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
65) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
66) N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
67) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
68) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-
25 urea;
69) N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
70) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
71) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
72) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-
30 urea;
73) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
74) N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
75) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
76) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-
35 urea;
77) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(benzothiophen-2-
yl)-urea;

- [illegible]

- [illegible]

- 116) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-morpholinophenyl)urea;
- 117) N-[4-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)phenyl]-N-methyl acetamide;
- 5 118) N-(2-{[cyclohexyl(methyl)amino]methyl}phenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 119) N-[3-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)-4-methoxyphenyl]acetamide;
- 120) N-(5-isopropyl-1,3-thiazol-2-yl)-4-(4-methoxyphenyl)-1-piperazine carboxamide;
- 10 121) N-(2-furylmethyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 122) N-(4-fluorophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 15 123) N-(2-methoxybenzyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 124) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[2-(1-methyl-1H-pyrrol-2-yl)ethyl]urea;
- 125) N-(3,4-dimethoxybenzyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 20 126) N-(5-isopropyl-1,3-thiazol-2-yl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane-8-carboxamide;
- 127) n-(5-isopropyl-1,3-thiazol-2-yl)-1,4-dioxo-8-azaspiro[4.5]decane-8-carboxamide;
- 25 128) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[2-(1-piperidinyl)ethyl]urea;
- 129) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[2-(1-morpholinyl)ethyl]urea;
- 130) 4-(4-fluorophenyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperazine carboxamide;
- 30 131) N-[4-(4-chlorophenyl)-3-ethyl-5-isoxazolyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 132) 4-[(4-fluorophenyl)(hydroxy)methyl]-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperidine carboxamide;
- 35 133) N-(3-ethynylphenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 134) N-(2-methoxy-3-fluorophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;

- 135) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-oxo-1-piperidinyl)urea;
- 136) N-(3-acetylaminophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 5 137) N-[3-(2-furyl)-1H-pyrazol-5-yl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 138) N-{4-[ethyl(isopropyl)amino]phenyl}-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 139) N-(1,3-benzodioxol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 10 140) 5-({[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}amino)-1-phenyl-1H-pyrazole-4-carboxamide;
- 141) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-pyridinylmethyl)urea;
- 15 142) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-pyrazinyl)urea;
- 143) n-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-phenyl-1,3,4-oxadiazol-2-yl)urea;
- 144) N-(5-isopropyl-1,3-thiazol-2-yl)-4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-piperidine carboxamide;
- 20 145) N-(1,3-benzothiazol-6-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 146) N-(1,3-dimethyl-1H-pyrazol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 25 147) N-(3-phenyl-1-methyl-1H-pyrazol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 148) N-(5-isopropyl-1,3-thiazol-2-yl)-3-hydroxy-1-piperidine carboxamide;
- 149) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)urea;
- 30 150) N-(5-isopropyl-1,3-thiazol-2-yl)-4-benzyl-1-piperazine carboxamide;
- 151) N-(5-isopropyl-1,3-thiazol-2-yl)-4-methyl-1-piperazine carboxamide;
- 35 152) 4-hydroxy-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperidine carboxamide;
- 153) N-(5-isopropyl-1,3-thiazol-2-yl)-3-azabicyclo[3.2.2]nonane-3-carboxamide;

- 154) N-(5-isopropyl-1,3-thiazol-2-yl)-4-(4-acetylphenyl)-1-piperazine carboxamide;
- 155) 4-[bis(4-fluorophenyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperazine carboxamide;
- 5 156) N-(5-isopropyl-1,3-thiazol-2-yl)-4-oxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide;
- 157) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5,6,7,8-tetrahydro-1-naphtalenyl)urea;
- 158) N-(4-phenyl-2-thiazolyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 10 159) 4-(4-fluorobenzoyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperidine carboxamide;
- 160) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-1,3-dihydro-2-benzofuran-5-yl)urea;
- 15 161) N-(5-isopropyl-1,3-thiazol-2-yl)-4'-(2-pyrimidinyl)-1-piperazine carboxamide;
- 162) N-(5-isopropyl-1,3-thiazol-2-yl)-3-oxo-3,4-dihydro-1(2H)-quinoxaline;
- 163) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1H-indazol-6-yl)urea;
- 20 164) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-chlorobenzyl)urea;
- 165) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dichlorobenzyl)urea;
- 25 166) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-fluorobenzyl)urea;
- 167) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-dichlorobenzyl)urea;
- 168) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-difluorobenzyl)urea;
- 30 169) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-difluorobenzyl)urea;
- 170) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-2,6-difluorobenzyl)urea;
- 35 171) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(4-hydroxy-3-methoxy)benzyl]urea;
- 172) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-methyl-2-furyl)urea;

- 173) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methylsulfonylbenzyl)urea;
- 174) N-[(1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 5 175) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-chlorobenzyl)urea;
- 176) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-pyridinylmethyl)urea;
- 177) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-dimethoxybenzyl)urea;
- 10 178) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-pyridinylmethyl)urea;
- 179) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-trifluorobenzyl)urea;
- 15 180) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4,5-trimethoxybenzyl)urea;
- 181) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dimethoxybenzyl)urea;
- 182) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-dimethylaminobenzyl)urea;
- 20 183) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-dimethoxybenzyl)urea;
- 184) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(2-chloro-6-phenoxy)benzyl]urea;
- 25 185) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]urea;
- 186) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(3-hydroxy-4-methyl)phenyl]urea;
- 187) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[4-(1H-benzimidazol-2-yl)phenyl]urea;
- 30 188) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-phenyl-1H-pyrazol-5-yl)urea;
- 189) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methyl-6-quinolinyl)urea;
- 35 190) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[4-(cyanomethyl)phenyl]urea;
- 191) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-quinolinyl)urea;

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- 192) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1-oxo-2,3-dihydro-1H-inden-5-yl)urea;
- 193) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-oxo-1,3-dihydro-2-benzofuran-5-yl)urea;
- 5 194) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-oxo-5,6,7,8-tetrahydro-2-naphtalenyl)urea;
- 195) methyl-3-([(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl)amino)-4-methylbenzoate;
- 196) methyl-4-([(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl)amino)-3-methylbenzoate;
- 10 197) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-imidazo[1,2-a]pyridin-2-yl-phenyl)urea;
- 198) ethyl-4-([(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl)amino)benzoate;
- 15 199) (2R)-1-benzyl-2-([(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl)amino)propanamide;
- 200) 2-hydroxy-5-([(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl)benzoic acid;
- 201) 2-chloro-5-([(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl)amino)benzoic acid;
- 20 202) 3-([(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl)amino)benzoic acid;
- 203) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-methyl-3-isoxazolyl)urea;
- 25 204) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,6-dimethoxyphenyl)urea;
- 205) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,3-dimethoxybenzyl)urea;
- 206) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-difluorobenzyl)urea;
- 30 207) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dimethylphenyl)urea;
- 208) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1H-benzimidazol-5-yl)urea;
- 35 209) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(R)-phenylglycinamido]urea;

- 210) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-phenoxyacetamido)urea;
- 211) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(S)-phenylglycinamido]urea;
- 5 212) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-{2-[(1-methyl-1H-imidazol-2-yl)methoxy]phenyl}urea;
- 213) N-(3-iodophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 214) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[3-(3-methoxy-1-propynyl)phenyl]urea;
- 10 215) N-{3-[3-(dimethylamino)-1-propynyl]phenyl}-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 216) N-[4-{{{(5-isopropyl-1,3-thiazol-2-yl)amino}carbonyl}amino}phenyl]methanesulfonamide;
- 217) 2-[3-{{{(5-isopropyl-1,3-thiazol-2-ylamino}carbonyl}amino)anilino}acetamide];
- 15 218) N-[3-(3-hydroxy-1-butynyl)phenyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 219) N-(imidazo[1,2-a]pyridin-2-yl-methyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 20 220) 2-{{{[(5-isopropyl-1,3-thiazol-2-yl)amino}carbonyl](2-propynyl)amino}methyl}benzenesulfonamide;
- 221) N-(1H-indol-6-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 222) N-[(1S)-2-hydroxy-1-phenylethyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 25 223) N-(1H-indol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 224) N-[(1R)-2-hydroxy-1-phenylethyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 30 225) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-butylurea;
- 226) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-benzoylurea;
- 227) N-(5-methyl-1,3-thiazol-2-yl)-N'-(2,6-dimethylphenyl)urea;
- 228) N-(5-methyl-1,3-thiazol-2-yl)-N'-benzylurea;
- 35 229) N-(5-methyl-1,3-thiazol-2-yl)-N'-butylurea;
- 230) N-(5-methyl-1,3-thiazol-2-yl)-4-morpholinecarboxamide;
- 231) N-(5-methyl-1,3-thiazol-2-yl)-N'-phenylurea;
- 232) N-(5-methyl-1,3-thiazol-2-yl)-N'-(4-methoxybenzyl)urea;

233) N-(5-methyl-1,3-thiazol-2-yl)-N'-(4-fluorophenyl)urea;

234) N-[(1-ethyl-2-pyrrolidinyl)methyl]-N'-(5-methyl-1,3-thiazol-2-yl)urea;

235) N-(5-methyl-1,3-thiazol-2-yl)-N'-(5-hydroxy-1H-pyrazol-3-yl)urea;

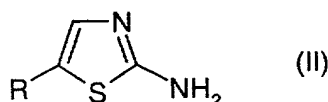
236) N-(5-methyl-1,3-thiazol-2-yl)-N'-(3-pyridinyl)urea;

237) N-(4-fluorophenyl)-N'-(5-methyl-1,3-thiazol-2-yl)urea.

14. A process for preparing a compound of formula (I), as defined in claim 7, which process comprises:

a) when R_2 is a hydrogen atom

reacting a compound of formula (II)



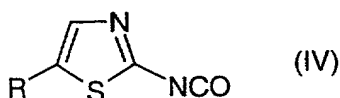
wherein R is as defined in claim 7, with a compound of formula (III)



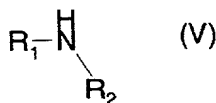
wherein R_1 is as defined in claim 7; or

b) when R_2 is as defined in claim 7

reacting a compound of formula (IV)

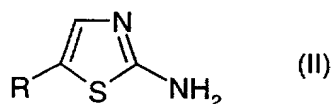


wherein R is as defined in claim 7, with a compound of formula (V)

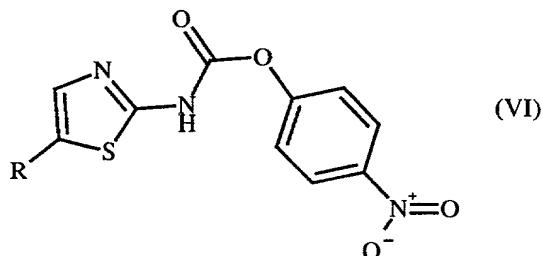


wherein R_1 and R_2 are as defined in claim 7; and, if desired, converting a 2-ureido-1,3-thiazole derivative of formula (I) into another such derivative of formula (I), and/or into a salt thereof.

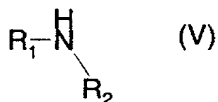
15. A process for preparing a compound of formula (I), as defined in claim 7, which process comprises reacting a compound of formula (II)



wherein R is as defined in claim 7, with 4-nitrophenyl-chloroformate, or a polymer supported form of it, thus obtaining a compound of formula (VI), or a polymer supported form of it,



wherein R is as defined in claim 7; and reacting a compound of formula (VI) with a compound of formula (V)



wherein R_1 and R_2 are as defined in claim 7; and, if desired, converting a 2-ureido-1,3-thiazole derivative of formula (I), or a polymer supported form of it, into another such derivative of formula (I), and/or into a salt thereof.

16. A pharmaceutical composition comprising one or more pharmaceutically acceptable carriers and/or diluents and, as the active principle, an effective amount of a compound of formula (I) as defined in claim 1.

Declaration and Power of Attorney for Patent Application Dichiarazione e procura ai fini della domanda di brevetto

Italian Language Declaration

Il sottoscritto inventore dichiara che.

As a below named inventor, I hereby declare that:

La propria residenza, recapito postale e cittadinanza corrispondono a quanto indicato in calce, sotto la propria firma.

My residence, post office address and citizenship are as stated next to my name

Ritiene di essere il primo ed unico inventore originale (se viene elencato in calce un solo nominativo) o il coninventore primo ed originale (se è elencato più di un nominativo) dell'oggetto rivendicato e per il quale il sottoscritto presenta domanda di brevetto. La invenzione in questione è chiamata

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

2-Ureido-thiazole derivatives, process

for their preparation, and their use as

antitumor agents

e la sua descrizione è allegata alla presente Dichiarazione a meno:

the specification of which

☐ è qui allegato

☐ is attached hereto

☐ Il _____

☒ was filed on 27 October 1999

è stata depositata una domanda di brevetto statunitense numero o una domanda di brevetto internazionale PCT numero

as United States Application Number or PCT International Application Number

PCT/EP99/08307

_____ che è stata modificata il

_____ and was amended on

_____ (se applicabile)

_____ (if applicable)

Il sottoscritto dichiara in oltre di aver letto e compreso il contenuto della descrizione identificata in precedenza, rivendicazioni comprese, come modificati dall'eventuale modifica summenzionata.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above

Il sottoscritto riconosce l'obbligo di rivelare informazioni essenziali ai fini della determinazione della brevettabilità ai sensi del Titolo 37, Codice dei Regolamenti Federali, § 1.56.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56

Italian Language Declaration

Il sottoscritto rivendica con la presente la priorità prevista dal Titolo 35, Codice degli Stati Uniti, § 119(e)-(d) o § 365(b) in relazione a qualsiasi domanda o domande estere di brevetto o certificato di inventore, o dal Titolo 35, § 365(a) degli stessi Codice in relazione a qualsiasi domanda internazionale PCT nella quale è designato almeno un paese diverso dagli Stati Uniti, i suddetti domande e certificati essendo elencati sotto, e, spuntando le seguenti caselle, ha anche identificato sotto qualsiasi domanda estera di brevetto o certificato di inventore, o domanda internazionale PCT, la cui data di deposito preceda quella dalla domanda per la quale è rivendicata la priorità.

I hereby claim foreign priority under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below, and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed

Prior Foreign Application(s)
(Domande Estere Anteriori)

Priority claimed
Diritto di priorità
rivendicato

9823873.6 Great Britain
(Number) (Country)
(Numero) (Nazione)

30 October 1998
(Day/Month/Year Filed)
(Giorno/Mese/Anno di deposito)

☒ ☐
Yes No
Si No

(Number) (Country)
(Numero) (Nazione)

(Day/Month/Year Filed)
(Giorno/Mese/Anno di deposito)

☐ ☐
Yes No
Si No

Il sottoscritto rivendica con la presente i benefici previsti dal Titolo 35, Codici degli Stati Uniti, § 119(e), in relazione a qualsiasi domanda o domande provvisorie degli Stati Uniti elencate sotto

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below

(Application No.)
(N° della domanda)

(Filing Date)
(Data di deposito)

(Application No.)
(N° della domanda)

(Filing Date)
(Data di deposito)

Il sottoscritto rivendica con la presente i benefici previsti dal Titolo 35, Codice degli Stati Uniti, § 120, in relazione a qualsiasi domanda o domande statunitensi, o dal Titolo 35, § 365(c) degli stessi Codice in relazione a qualsiasi domanda internazionale PCT nella quale sono designati gli Stati Uniti, i suddette domande essendo elencate sotto e, nella misura in cui l'oggetto di ciascuna rivendicazione di questa domanda non sia stato esposto nella domanda statunitense o internazionale PCT anteriore nel modo previsto dal primo paragrafo del Titolo 35, Codice degli Stati Uniti, § 112, riconosce l'obbligo di rivelare informazioni essenziali ai fini della determinazione della brevettabilità ai sensi del Titolo 37, Codici dei Regolamenti Federali, § 1.56, le quali diventino disponibili durante il periodo compreso tra la data di deposito della domanda anteriore e la data di deposito nazionale o internazionale PCT della presente domanda

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application

(Application No.)
(N° della domanda)

(Filing Date)
(Data di deposito)

(Status) (patented, pending, abandoned)
(Stato) (concessione di brevetto, in corso di esame, abbandono)

(Application No.)
(N° della domanda)

(Filing Date)
(Data di deposito)

(Status) (patented, pending, abandoned)
(Stato) (concessione di brevetto, in corso di esame, abbandono)

Con la presente, il sottoscritto dichiara veritiere tutte le affermazioni contenute in questa domanda in relazione alle proprie conoscenze e di ritenere vere tutte le affermazioni o informazioni presentate. Dichiara inoltre che tali asserzioni sono state espresse nella piena consapevolezza che le dichiarazioni intenzionalmente false sono punibili con una poutle, l'incarcerazione o entrambe, ai sensi della Sezione 1001 del Titolo 18 del Codice degli Stati Uniti e che tali dichiarazioni intenzionalmente false possono mettere a repentaglio la validità della domanda o di qualsiasi brevetto ruasciato in merito.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Italian Language Declaration

PROCURA: Il sottoscritto inventore nomina con la presente il seguente avvocato o avvocati e/o agente o agenti al fine di istruire questa pratica e di condurre tutte le operazioni ad essa pertinenti presso l'Ufficio dei Brevetti e Marchi di Fabbrica: (Elencare il nome ed il numero di matricola).

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (list name and registration number)

Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913; C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No. 25,599; Arthur I. Neustadt, Reg. No. 24,854; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870; Robert T. Pous, Reg. No. 29,099; Charles L. Gholz, Reg. No. 26,395; William E. Beaumont, Reg. No. 30,996; Jean-Paul Lavalleye, Reg. No. 31,451; Stephen G. Baxter, Reg. No. 32,884; Richard L. Treanor, Reg. No. 36,379; Steven P. Weihrauch, Reg. No. 32,829; John T. Goolkasian, Reg. No. 26,142; Richard L. Chinn, Reg. No. 34,305; Steven E. Lipman, Reg. No. 30,011; Carl E. Schlier, Reg. No. 34,426; James J. Kulbaski, Reg. No. 34,648; Richard A. Neifeld, Reg. No. 35,299; J. Derek Mason, Reg. No. 35,270; Surinder Sachar, Reg. No. 34,423; Christina M. Gadiano, Reg. No. 37,628; Jeffrey B. McIntyre, Reg. No. 36,867; William T. Enos, Reg. No. 33,128; Michael E. McCabe, Jr., Reg. No. 37,182; Bradley D. Lytle, Reg. No. 40,073; and Michael R. Casey, Reg. No. 40,294, with full powers of substitution and revocation.

Inviare le corrispondenza a:

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Nome e cognome dell'unico o del primo inventore	Full name of sole or first inventor
<u>Paolo</u>	<u>Paolo Pevarello</u>
Firma dell'inventore	Inventor's signature
<u>Paolo Pevarello</u>	<u>Paolo Pevarello</u>
Data	Date
	<u>12 March 2001</u>
Residenza	Residence
	<u>Pavia, Italy</u>
Cittadinanza	Citizenship
	<u>Italian</u>
Recapito postale	Post Office Address
	<u>Piazza San Pietro in Ciel d'Oro, 7/A,</u>
	<u>27100 Pavia, Italy</u>
Nome e cognome dell'eventuale secondo coinventore	Full name of second joint inventor, if any
	<u>Raffaella Amici</u>
Firma del secondo coinventore	Second inventor's signature
<u>Raffaella</u>	<u>Raffaella Amici</u>
Data	Date
	<u>12 March 2001</u>
Residenza	Residence
	<u>Piacenza, Italy</u>
Cittadinanza	Citizenship
	<u>Italian</u>
Recapito postale	Post Office Address
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(Fornire le stesse informazioni e le firme del terzo e degli ulteriori coinventori)

(Supply similar information and signature for third and subsequent joint inventors)

Italian Language Declaration

Nome per intero di un eventuale terzo co-inventore		Full name of third joint inventor, if any	
300		Gabiella Traquandi	
Firma del Terzo Inventore	Data	Third inventor's signature	Date
		Gabiella Traquandi	12 March 2001
Residenza		Residence	
		Milano, Italy	ITX
Cittadinanza		Citizenship	
		Italian	
Recapito postale		Post Office Address	
		Via F. Cilea, 106, 20151 Milano, Italy	
Nome per intero di eventuale quarto co-inventore		Full name of fourth joint inventor, if any	
400		Manuela Villa	
Firma Quarto Inventore	Data	Fourth inventor's signature	Date
		Manuela Villa	12 March 2001
Residenza		Residence	
		Lurago d'Erba (Como), Italy	ITX
Cittadinanza		Citizenship	
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		Via San Bernardino, 12, 22040 Lurago	
		d'Erba (Como), Italy	
Nome per intero di un eventuale quinto co-inventore		Full name of fifth joint inventor, if any	
500		Anna Vulpetti	
Firma Quinto Inventore	Data	Fifth inventor's signature	Date
		Anna Vulpetti	12 March 2001
Residenza		Residence	
		Brugherio (Milano), Italy	ITX
Cittadinanza		Citizenship	
		Italian	
Recapito postale		Post Office Address	
		Via Volturmo Portici/2 80, 20047	
		Brugherio (Milano), Italy	
Nome per intero di un eventuale sesto co-inventore		Full name of sixth joint inventor, if any	
600		Antonella Isacchi	
Firma del Sesto Inventore	Data	Sixth inventor's signature	Date
		Antonella Isacchi	12 March 2001
Residenza		Residence	
		Milano, Italy	ITX
Cittadinanza		Citizenship	
		Italian	
Recapito postale		Post Office Address	
		Via Montecatini, 14, 20144 Milano,	
		Italy	

(Si prega di fornire simili informazioni e firme per il terzo e gli eventuali ulteriori co-inventori)

(Supply similar information and signature for third and subsequent joint inventors)